CHEMICAL MANUFACTURERS ASSOCIATION

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VIA FEDERAL EXPRESS

Dr. C.W. Jameson
National Toxicology Program (MD EC-14)
Report on Carcinogens
79 Alexander Drive
Building 4401, Room 3127
P.O. Box 12233
Research Triangle Park, NC 27709

Re: Review of Crystalline Silica for NTP's Biennial Report on Carcinogens

Dear Dr. Jameson:

The Chemical Manufacturers Association (CMA) Crystalline Silica Panel has participated actively over the past decade in numerous Federal and State reviews of the toxicity of crystalline silica. In light of the National Toxicology Program's (NTP's) decision to review its Report on Carcinogen's listing of respirable silica, we asked Dr. John F. Gamble of Exxon Biomedical Sciences to review the available epidemiology. Enclosed is his just-completed review. This review was prepared for the Silica Coalition and the Crystalline Silica Panel. Also enclosed are three commentaries on silica animal studies to further aid NTP's consideration of crystalline silica.

On March 10th, the Panel sent NTP a review of crystalline silica epidemiology studies by the Institute of Occupational Medicine (IOM). We urge NTP's close consideration of both the IOM and Gamble reviews, as we believe the epidemiology data do not provide "sufficient evidence" of a "causal relationship" as is required for NTP to find that crystalline silica is known to be a human carcinogen.

NTP BACKGROUND

NTP listed respirable crystalline silica as a substance "reasonably anticipated" to be a carcinogen in its Sixth Annual Report (1991). NTP's Summary found "sufficient" evidence of the carcinogenicity of respirable silica in animals, but agreed with the 1987 International Agency for Research on Cancer (IARC) conclusion that the human evidence was "limited." NTP noted specifically (at p. 358) that "[o]nly rarely were data obtained on smoking and on potential confounding exposures and the comparability of the referent population assured."

NTP's criteria for listing as a known human carcinogen require a finding of "sufficient evidence from studies in humans which indicates a causal relationship between exposure to the...substance...and

human cancer." "Sufficient" evidence is distinguished in the criteria from "limited" human evidence that does not warrant a "known" carcinogen listing; "limited" human evidence exists when a "causal interpretation is credible but...alternative explanations such as chance, bias or confounding factors could not adequately be excluded."

NTP's reconsideration of crystalline silica follows IARC's reclassification of silica. It is significant that the IARC reclassification occurred only after a sharply divided vote of its expert committee and that the reclassification was unusually and carefully circumscribed. Of the nineteen scientists on the IARC Working Group, only ten supported the reclassification (seven voted against the reclassification, one abstained, and one was not present). And, the reclassification was based on an evaluation (all emphases added) that found "sufficient evidence in humans for the carcinogenicity of inhaled crystalline silica in the forms of quartz or cristobalite *from occupational sources*." The Working Group further limited its evaluation by noting:

> In making the overall evaluation the Working Group noted that carcinogenicity was *not detected in all industrial circumstances* studied. Carcinogenicity may be dependent on inherent characteristics of crystalline silica or external factors affecting its biological activity or distribution of its polymorphs.

Thus, even the far from unanimous IARC evaluation included qualifiers not typically found in the Agency's evaluations. It is, therefore, particularly important for NTP to conduct its own careful, independent assessment.

DR. GAMBLE'S REVIEW

Dr. Gamble was an observer at the IARC Working Group meeting on silica. He has recently completed the enclosed review of all the epidemiology studies reviewed by IARC, as well as a few more recently published studies. Dr. Gamble addresses two issues:

(1) Does the risk of lung cancer increase as silica exposures increase (the silica/lung cancer hypothesis)?

(2) Is silicosis a risk factor for lung cancer (the silicosis/lung cancer hypothesis)?

With respect to each inquiry, Dr. Gamble employs a weight-of-the-evidence approach and the Sir Bradford Hill causation criteria to determine whether there is a consistent pattern of associations of silica exposure, or silicosis, with lung cancer. In conducting this assessment, Dr. Gamble gives the greatest weight to those studies that are relatively free of confounding, bias or chance, thus paying close attention to the two issues raised by NTP in its prior review of silica, namely the need to control for worker smoking habits and the need for the exposed and unexposed cohorts to be otherwise comparable. This scientific approach corresponds with the legal parameters set forth for NTP listing that require a finding of "sufficient evidence" of a "causal relationship" before a substance is found to be a known human carcinogen.

Applying the foregoing criteria, Dr. Gamble identified twelve studies of quartz-exposed workers (two of which involved the same cohort) that qualified for inclusion in a weight-of-evidence review to test the silica/lung cancer hypothesis. Eight of these studies found no increased risk of lung cancer in the

high quartz-exposed group and no trend (or an inverse trend) for the risk of lung cancer to increase as silica exposure increased. Three of these studies showed a weak association between quartz exposure in the high exposure group and increased risk of lung cancer, but none of these associations was statistically significant. Only one of the studies showed a statistically significant association between lung cancer and exposure to quartz in the highest exposed group, and that association no longer was significant when an adjustment for silicosis was made in a follow-up study of the same cohort. These findings, Dr. Gamble notes, contrast sharply with the strong associations between silica exposure and non-malignant respiratory disease found in many of the same studies.

The weight of evidence from these studies, Dr. Gamble concludes, does not support the silica/lung cancer hypothesis because -- in almost all cases -- the associations, when present at all, are weak, and there is no consistent finding of a gradient for the risk of lung cancer to increase as silica exposures increase. To the contrary, if anything, these studies show a consistent pattern of no significant association between quartz exposure and increased risk of lung cancer. The studies of silica-exposed workers, therefore, clearly "do not confirm an increased risk of cancer in exposed humans" and are "insufficient to classify [quartz] as a confirmed human carcinogen."

Likewise, the studies of silicotics do not show silicosis to be a risk factor for lung cancer. Eleven silicotic studies (involving nine separate cohorts) meet the criteria identified by Dr. Gamble for inclusion in a weight-of-evidence evaluation. For the reasons outlined briefly above and discussed more fully in Dr. Gamble's Review, registry-based studies -- with their large potential for bias, confounding, and misdiagnosis -- could not contribute meaningful information to the analysis.

For the silicosis/lung cancer hypothesis to be correct, Dr. Gamble points out, silicotics should have to show a strong and consistent increased risk of lung cancer when risks are evaluated by comparisons of:

(1) Silicotic vs. nonsilicotics;
(2) High severity of silicosis vs. low severity of silicosis; and,
(3) Silicotics with high exposure to silica vs. silicotics with low exposure to silica.

In fact, no such consistent increase in risk is found when making such comparisons. To the contrary, ten of eleven silicotic vs. non silicotic comparisons showed no statistically significant difference in lung cancer risk, and in three of the four studies where lung cancer risk was evaluated by severity of silicosis, there were no significant differences in lung cancer risk among subjects with the most severe grades of silicosis vs. those with less severe grades. Moreover, none of the studies where exposure information for the silicotics was available showed a significant trend for the risk of lung cancer to increase as silica exposure increased. Indeed, in most cases, there was a nonsignificant inverse trend. As with the silica/lung cancer hypothesis, Dr. Gamble concludes, the weight of the evidence does not support the silicosis/lung cancer hypothesis.

ANIMAL STUDIES OF CRYSTALLINE SILICA

Significant commentary on the silica animal studies has been published since the last NTP review. That commentary has emphasized a number of reasons why the animal evidence may not be relevant to humans, including the fact that silica has been found to induce tumors in no species other than the rat -- including the mouse, guinea pig and Syrian hamster -- and there is an absence of a dose-response relationship in the rat studies.

We enclose copies of three such commentaries to further aid and inform NTP's review. As the enclosed review by Drs. L. Martin Holland and Brooke T. Mossman points out, "there is a strong possibility that the carcinogenic response in the rat is a specific and even unique phenomenon peculiar to that species." (Page 2) Dr. Holland elaborates on this conclusion in his 1995 article from Applied Occupational and Environmental Hygiene. Dr. J. L. Mauderly's 1997 review in the NIEHS journal Environmental Health Perspectives details why "[f]or inhaled particles, increasing evidence shows that the proliferative and neoplastic responses of the rat lung to heavy, chronic exposures may not serve as good models for lung responses of humans to lesser exposures." (Page 1337)

* * * * *

In submitting these commentaries, we are not suggesting that NTP should revise its previous conclusion that there is sufficient evidence of crystalline silica carcinogenicity in animals. We do believe, however, that the limited relevance to humans of the rat studies upon which that conclusion was based further underscores the need to review the epidemiologic studies with great care in assessing whether they constitute sufficient evidence of carcinogenicity to humans. We believe Dr. Gamble's review provides such a careful assessment and urge your close attention to it.

If the Panel can provide any further information, please contact Elizabeth Festa Watson, Panel Manager, at 703-741-5629, or elizabeth_watson@cmahq.com.

Sincerely yours,

Courtney M. Price
Vice President, CHEMSTAR

cc(w/enc): Dr. Larry G. Hart, NTP
(via FedEx)

IS SILICA A HUMAN CARCINOGEN?
A WEIGHT-OF-THE-EVIDENCE REVIEW

For the Silica Coalition

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98TP 105

TABLE OF CONTENTS

PAGE

EXECUTIVE SUMMARY

In October 1996, a Working Group of the International Agency for Research on Cancer (IARC) -- in a divided vote -- concluded that there is sufficient evidence that crystalline silica in the form of quartz or cristobalite inhaled from occupational sources is carcinogenic to humans. The present Review reexamines this issue by addressing two related questions: (1) Does the risk of lung cancer increase as silica exposures increase (the "silica/lung cancer hypothesis")? (2) Is silicosis a risk factor for lung cancer (the "silicosis/lung cancer hypothesis")?

Studies of silica-exposed workers were included in this weight-of-evidence review if they were relatively free of bias and confounding, and if they evaluated exposure-response using appropriate referent groups. Thirteen studies of silica-exposed workers (two of which involved the same cohort) were identified that met most of these criteria.

Eight of these studies found no increased risk of lung cancer in the high quartz-exposed group and no trend (or an inverse trend) for the risk of lung cancer to increase as silica exposure increased. Three of these studies showed a weak association between quartz exposure in the high exposure group and increased risk of lung cancer, but none of those associations was statistically significant. Only one of the studies showed a statistically significant association between lung cancer and exposure to quartz in the highest exposed group, and that association no longer was significant when an adjustment for silicosis was made in a follow-up study of the same cohort. These findings contrast sharply with the strong associations between silica exposure and non-malignant respiratory disease found in many of the same studies. In addition, one study showed a suggestive increased risk of lung cancer among diatomaceous earth workers with high exposure to cristobalite, but the true association is unclear because of potential confounding and misclassification bias. And a second study found a relatively weak association between increased lung cancer risk and employment in pottery jobs where there may have been exposure to cristobalite.

The weight of the evidence from these studies does not support the silica/lung cancer hypothesis because -- in almost all cases -- the associations, when present at all, are weak, and there is no consistent finding of a gradient for the risk of lung cancer to increase as silica exposures increase.

Silicosis can be viewed in one sense as a surrogate measure of silica dose and in another sense as a potential independent risk factor for lung cancer. Studies of silicotics should meet the same criteria for inclusion in a weight-of-evidence evaluation as studies of silica-exposed workers, with the additional requirement that the diagnosis of silicosis should not be biased. Eleven studies (involving nine separate cohorts) meet these criteria. If the silicosis/lung cancer hypothesis is correct, silicotics should show a strong and consistent increased risk of lung cancer

when risks are evaluated by comparisons of (1) silicotics vs. nonsilicotics, (2) high severity of silicosis vs. low severity of silicosis, and (3) silicotics with high exposure to silica vs. silicotics with low exposure to silica.

Ten of eleven silicotic vs. nonsilicotic comparisons showed no statistically significant difference in lung cancer risk, and in three of the four studies where lung cancer risk was evaluated by severity of silicosis, there were no significant differences in lung cancer risk among subjects with the most severe grades of silicosis vs. those with less severe grades. Moreover, none of the studies where exposure information for the silicotics was available showed a significant trend for the risk of lung cancer to increase as exposure increased. Indeed, in most cases, there was a non-significant inverse trend.

The weight of the evidence does not support the silicosis/lung cancer hypothesis.

After controlling for chance, confounding, and bias, the weight of the evidence indicates that neither silica exposure nor silicosis increases the risk of lung cancer.

I. INTRODUCTION

This Review addresses two related questions:

1. The silica/lung cancer hypothesis: Does the risk of lung cancer increase as silica exposure increases?

2. The silicosis/lung cancer hypothesis: Is silicosis a risk factor for lung cancer?

In October 1996, an IARC Working Group concluded in a divided vote that there is "*sufficient evidence* in humans for the carcinogenicity of inhaled crystalline silica in the form of quartz or cristobalite from occupational sources." This conclusion was set forth in a Monograph published in 1997. IARC Monographs purport to assess the "strength of the available evidence that certain exposures could alter the incidence of cancer in humans." Studies to be included in this assessment should, according to IARC and common practice, take into account bias, confounding, and chance; "lack of clarity" on any of these aspects of individual studies reduces the "weight given to it" in the final evaluation. After the quality of individual studies is assessed, several criteria for causality are considered. These include a strong association, consistency, and biological gradient (or exposure-response) (IARC, 1997; Hill, 1965; HEW, 1964).

The summary that IARC provides of its approach to a "strength of the evidence" evaluation is not entirely clear, but it seems to assume that the evidence of human carcinogenicity can be deemed *sufficient* if there are one or more unconfounded studies showing a tendency for the relative risk of cancer to be increased in the exposed group, or as exposure increases, even though that association or tendency is weak and is not seen in other studies

(IARC, 1997). We do not believe that such an approach to determining causality based on epidemiological studies is appropriate.

This Review will use a "weight-of-the-evidence" approach. The weight of the evidence is increased in favor of a causal association when there is: (1) a consistent pattern of moderate-to-strong associations between exposure and increased cancer risk; and (2) consistent biological gradients in studies that are relatively free of confounding, bias, and chance. A single study suggesting an association between exposure to the agent and increased risk of cancer should not result in a finding of *sufficient* evidence of human carcinogenicity when other studies that meet the criteria for evaluation do not show an association with exposure to the agent or an exposure-response gradient.

The second question is added to this Review for further insight into the silica/lung cancer hypothesis. If silica is a carcinogen, then silicotics (who are among those with the highest silica exposure and/or the greatest susceptibility) should consistently be at increased risk of lung cancer. If they are not, the coherence of the silica/lung cancer hypothesis must be called into question.

This Review is divided into three parts.

Section II discusses the criteria for selection of studies. These criteria were formalized by IARC, and are meant to screen out studies that are subject to misinterpretation because of chance, confounding, or bias. IARC (1997) did not consistently apply all these criteria in deciding which studies provided the least confounded examination of a potential association, as IARC was concerned largely with confounding from occupational carcinogens. In addition, we have placed more emphasis than IARC on the principle that, to be truly informative, a study testing the silica/lung cancer hypothesis should be relatively free of other biases and also should assess exposure-response gradients. For these reasons, the lists of studies considered important by IARC and in this Review will differ to some extent.

Section II also discusses the special considerations that apply in selecting studies that address the silicosis/lung cancer hypothesis. These studies comprise a group of registry-based and nonregistry-based studies with different methods for diagnosing silicosis (e.g., autopsy, radiology, compensation). Some studies provide evidence relevant to testing both the silica/lung cancer hypothesis and the silicosis/lung cancer hypothesis -- *i.e.*, silicotics are identified and their risks assessed as a separate group within a cohort of silica-exposed workers.

Section III evaluates individual studies to determine whether they do or do not meet the selection criteria and summarizes the principal findings of the studies that do meet the criteria. All the studies that IARC (1997) considered as providing the "least confounded examinations of an association between silica exposure and cancer risk" are evaluated in light of the criteria for selection set forth in Section II. Some studies that IARC evaluated but excluded from its list of

least confounded studies were re-evaluated. These are added to the list of relevant studies if they satisfy the criteria for inclusion. Two studies published after the IARC Working Group meeting satisfy some of the criteria and are therefore considered as well. The reasoning behind the determination of relevance is provided for each study.

Finally, Section IV applies generally accepted causal criteria (Hill, 1965; HEW, 1964) to the studies that were selected in Section III in order to reach a weight-of-the-evidence judgment about whether there is sufficient evidence of (1) an association between silica exposure and increased risk of lung cancer, or (2) an association between silicosis and increased risk of lung cancer.

II. CRITERIA FOR SELECTION OF STUDIES

To be useful in a weight-of-evidence review of the possible carcinogenicity of silica and to assist in the interpretation of epidemiological studies, it is necessary to "take into account the possible roles of bias, confounding, and chance" (IARC, 1997). That is, each study must: (a) not be confounded by factors such as smoking, occupational carcinogens, or dust; and (b) be free of significant bias such as selection or enumeration bias or diagnostic bias in identifying silicotics. Of course, for there to be an association it should not be a random occurrence, so the role of chance is also important. These criteria should in large part be satisfied. No epidemiology study is likely to meet all these criteria, but a partial failure should be of such a minor nature that an unambiguous interpretation can be made, and any confounding or bias would not materially change the results.

For purposes of the present Review, two elements of the criteria relating to confounding, bias, and chance have been emphasized more than they were in the IARC Monograph.

One is that appropriate referent groups should be used. In practical terms this generally means a less exposed group from the same universe (or cohort) as the exposed group.

The second is that there should be an analysis of exposure-response (E-R) gradients. E-R is an important causal criterion that is a specific test of the hypothesis; it may also provide some protection against confounding and bias if the referent group is appropriate.

Studies of silicotics require a slightly different approach than silica studies. Registry studies of silicotics generally suffer from problems of bias and confounding -- particularly bias in the diagnosis of silicosis and incomplete enumeration of the exposed population. Accordingly, the unique problems of studies that address the silicosis/lung cancer hypothesis will be discussed separately.

The foregoing criteria will be applied to select the studies that will form the body of evidence on which to test the silica/lung cancer hypothesis and the silicosis/lung cancer

hypothesis. The failure to meet one or more of the criteria does not automatically disqualify a study from being considered in the weight-of-evidence analysis but may result in a lower weight being assigned to that study.

To test the hypotheses in a weight-of-evidence review, the studies were classified as "adequate" or "with significant limitations." Adequate studies are those that meet the criteria for testing the hypothesis. Only studies that meet the selection requirements can then be used in the evaluation under Hill's causal criteria. Judgment is necessary to decide which studies to include and which to exclude; the guidelines are not rigid. For example, statistical significance of the results is an important criterion. However, nonsignificant trends in the data in the smaller, less powerful studies may be important. Each criterion is discussed below.

A. Chance

A significance test assesses the probability p (or the plausibility) that there is no difference between cases and controls, or no difference between high and low exposed groups. The p value (or 95% confidence interval) is the probability that the observed outcome would have occurred by chance. The 95% CI says we are 95% confident that the true value of the risk ratio (OR, SMR) lies between the upper and lower bounds of the interval. One chance out of 20 is generally accepted as unlikely to be a random occurrence ($p = 0.05$).

A nonsignificant result ($p > 0.05$) means the data are compatible with the effect being due to chance; it does not mean there is no effect, or even that there is no causal association. It means that a causal relationship is not the most likely explanation. Associations that are highly significant ($p < 0.001$) are rarely to be doubted. Findings of less significance ($p < 0.05$) may be due to chance.

Note that p-values are commonly reported for tests such as tests of the departure of an odds ratio from unity or tests of an exposure-response trend. The p-value is a confounded mix of the magnitude of the effect measured and the precision of the estimate, which is a function of sample size (Lang, et al. 1998). A more informative approach is to present the two pieces of information separately. The two pieces are the size of the effect, such as the risk ratio, and the precision of the estimate as a confidence interval. In this Review, confidence intervals have been calculated if possible when they are not presented in the original paper.

One must not rely on statistical significance alone. For example, as discussed in Section III below, Chinese tungsten miners and iron-copper miners studied by McLaughlin et al. (1992) showed a statistically significant trend for the risk of lung cancer to decrease as cumulative exposure to silica increased, but it seems unlikely that increasing exposure to respirable silica protects against lung cancer. Chinese pottery workers studied by the same authors showed a nonsignificant trend ($p > 0.05$) for the risk of lung cancer to increase as cumulative exposure to silica increased. When the three cohorts are considered together, the significant negative trends

in the studies of tungsten and iron-copper miners detract from the slight evidence of a silica/lung cancer association arising from the nonsignificant positive trend in the pottery worker cohort.

B. Relative Lack of Confounding

Confounding is a particular kind of bias where a factor can cause the disease and is also unequally distributed among the exposed and unexposed populations. For example, smoking and radon at some exposure level may increase the risk of lung cancer. If radon is correlated with dust exposure, it will confound the lung cancer/dust exposure association, so that an increased lung cancer risk may be falsely attributed to dust exposure. Similarly, if smoking prevalence is higher in high-dust exposed groups than in low-dust exposed groups, a higher risk of lung cancer in high-dust exposed groups may be falsely attributed to dust exposure when in fact it is caused by smoking. IARC (1997) apparently selected studies to be given the most consideration largely on the basis of a lack of confounding from occupational carcinogens, commonly radon and asbestos. When lung cancer is the health effect of concern, the major potential confounding risk factors should include smoking as well as occupational carcinogens.

Three major confounders that potentially mask the true relationship between silica and lung cancer are discussed below -- namely, smoking, occupational carcinogens, and dust exposure.

1. Smoking

Potential confounding from smoking is a constant concern in assessing the risk of lung cancer -- with the likely bias of overestimating risk becoming more pronounced among those with long latency. Both smoking-related lung cancer and occupationally-related lung cancers have long latencies, and the two outcomes may be correlated. Thus, to avoid confounding when comparing exposed and unexposed groups, they should have similar latency and length of follow-up with adjustments for differences in smoking prevalence. In a study where the strength of association between silica exposure and lung cancer is weak (RR <2), relatively small differences in the prevalence and intensity of smoking between the exposed and unexposed groups could very well be a reasonable alternative causal hypothesis. An advantage of controls selected from the same workforce as the cases (internal controls or internal analysis) is that differences in smoking prevalence and other lifestyle characteristics are likely to be minimized.

The 1985 Surgeon-General's report on smoking comments that adjustment for differences in smoking patterns and depth of inhalation may cause a 2-fold excess in risk attributable to smoking, and the use of high-tar and nicotine cigarettes might increase the risk even more (HHS, 1985). These calculations suggest that if there is no control of smoking in the analysis, then smoking alone may increase the lung cancer risk somewhere between 20 and 100%. Or put another way, if the apparent association between silica exposure and increased lung cancer risk is weak, it may be explained by smoking rather than by exposure to silica.

Various methods have been used to adjust for smoking effects. In the complete absence of smoking data, the risks from other smoking-related diseases have been used to estimate smoking-related lung cancer effects indirectly (Steenland et al., 1984). Although labeled as a "method of control for smoking," this approach at best can provide only a rough idea as to whether smoking prevalence in the exposed workers may be high. Moreover, even this rough idea is unreliable because the risks of smoking-related diseases differ from one study to another, the number of deaths attributed to smoking differ from one disease to another, and the smoking attributable risk differs from one disease to another. The variability in these parameters makes the indirect assessment of smoking prevalence unreliable for a given study population. Some examples illustrating the range in SMRs for the same smoking-related diseases based on different studies are presented in the following table: One column shows the ranges of SMRs for various smoking-related diseases from eight studies summarized in the 1989 Surgeon General's Report on Smoking (HHS, 1989); another column shows the ranges of SMRs from four studies reviewed by Steenland et al. (1984); the last column shows the percent of deaths attributed to cigarette smoking in males (Shopland et al., 1991).

Cigarette Smokers SMRs

	Range of 8 Studies	**Range of 4 Studies**	**% of Deaths Attributable to Smoking in Men**
Cause of Death	**(HHS, 1989)**	**(Steenland et al., 1984)**	**(Shopland et al., 1991)**
Lung Cancer	3.6 - 15.9	7.6 - 14	90
Laryngeal Cancer	6.1 - 13.6	6.1 - 9.0	81
Esophageal Cancer	1.7 - 6.6	1.8 - 9.0	78
Bladder Cancer	0.7 - 3.0	1.9 - 3.0	48
Pancreatic Cancer	1.6 - 6.0	1.6 - 2.7	29
Kidney Cancer	1.1 - 1.6	1.3 - 2.5	48
Emphysema	--	0.6 - 12.3	
Bronchitis	--	2.9 - 24.7	
CVD	1.3 - 1.9	--	
CHD	1.3 - 2.1	1.5 - 2.0	

Another more useful means of accounting for smoking , the Axelson method (Axelson, 1978), uses the differences in smoking prevalence between study and control populations in an attempt to indirectly adjust for a smoking effect. This method, too, is limited because it makes no adjustment for the number of cigarettes smoked each day (*i.e.*, intensity), and the actual smoking prevalences in the exposed cohort are incompletely known, so the appropriate risk ratio remains a guess. Blue-collar worker populations usually have a higher prevalence of smoking, which commonly implies smoking more cigarettes and higher tar cigarettes. Time of exposure is another important component of E-R relationship; before the 1960s, both nonfiltered and high tar cigarettes were the norm if not the rule.

Nonetheless, the prevalence of smoking is generally the major determinant of differences in lung cancer risk due to smoking as shown in these sample calculations derived from Axelson (1978). Using RRs of 10 and 60 as extremes, and the indicated differences in prevalence of smoking, the proportion of lung cancers attributable to smoking ranges from 18 to 57% in these examples:

RR of Smoking Prevalence of Smoking in:		**Relative Risk of Lung Cancer Attributable to Smoking**	
Exposed	**Controls**	**RR=10**	**RR=60**
85%	70%	1.18	1.21
90%	65%	1.33	1.38
95%	60%	1.49	1.57

In light of the important role of smoking on lung cancer risk, the 1985 Surgeon-General's Report indicates that the "adjusted" lung cancer risk attributed to smoking should lie below the lower 95% confidence interval of the exposed workers' RR before one can exclude the role of smoking. Thus, if the lower 95% confidence interval is less than unity after subtracting the estimated effect from smoking, then smoking is a reasonable alternative hypothesis for the increased cancer risk seen in those workers.

2. Occupational Carcinogens

The major potential occupational confounders among silica-exposed workers include radon and arsenic (primarily in mining cohorts), asbestos (diatomaceous earth, dusty trades, Finnish silicotics), and PAHs (e.g., potteries in China). Such occupational confounders must be taken into account when interpreting studies in which the workers were potentially coexposed to an occupational carcinogen as well as to silica. The significance of the potential confounding, however, may depend on the study results. For example, since radon is likely to be correlated with dust exposure in certain mines, radon could be causing an increased risk of lung cancer as dust exposure increases, thereby confounding an apparent positive association between lung cancer and dust exposure. However, if no association is found between lung cancer and dust

exposure, confounding by radon is unlikely to be an issue, since it is counterintuitive to believe that radon is protective against lung cancer. Therefore, if radon and dust levels are positively correlated, as seems reasonable in mines, radon can be a confounder where there is an apparent positive exposure-response trend with increasing dust levels, but it is unlikely to be a confounder in the absence of such a trend. The same would be true in cases where increasing PAH or arsenic exposures may be correlated with increasing silica exposures, *i.e.*, exposures to arsenic or PAH are unlikely to produce negative confounding (be protective) when silica exposures increase.

3. Dust Exposure

Silica exposure and dust exposure are generally highly correlated, so silicotics will generally also have higher mean dust exposures than nonsilicotics. Therefore, in assessing E-R using severity of silicosis, the association of silicosis with lung cancer may be confounded because high dust levels (which are associated with increased severity of silicosis) also can produce reduced lung function, which is an independent risk factor for lung cancer (Carta et al., 1991; Nomura et al., 1991; Kuller et al., 1990; Anthonisen et al., 1989; Tockman et al., 1987; Skillrud et al., 1986). In such cases, the impaired lung function is largely attributable to the dust exposure, independent of its silica content. For example, Wiles et al. (1992) separated the effects of silicosis on lung function from the effects of cumulative dust exposure by closely matching silicotics with nonsilicotics on age, smoking and dust exposure. By controlling for dust exposure, they showed no difference in lung function between silicotics and nonsilicotics. Similar results are reported by others (Bucca et al., 1985; Irwig and Rocks, 1978). To avoid or ameliorate this confounding effect, it is helpful to adjust for silicosis in the analysis, or to compare separate E-R trends for nonsilicotics and silicotics. This is rarely done.

C. Relative Lack of Bias

Bias is consistent nonrandom error. An example is participation, volunteer, or selection bias -- as might occur if there is consistent participation of smokers in a voluntary surveillance program for silicotics, while nonsmokers without symptoms are less likely to volunteer or participate. By the same token, smokers are more likely to be awarded compensation when symptoms and lung function impairment are part of compensation criteria. Detection or volunteer bias can be avoided by complete enumeration of the exposed cohort.

The results from the Gillam et al. (1976) study of Homestake gold miners provide an example of the potential effects of incomplete enumeration and volunteer bias. Gillam et al. (1976) selected miners with ≥5 years tenure from a cross-sectional survey of volunteers conducted in 1960. When compared to the results from the McDonald et al. (1978) and Brown et al. (1986) studies of Homestake miners who had longer tenure, longer follow-up, higher cumulative exposures, and complete enumeration, the SMRs in the study by Gillam et al. (1976) were considerably higher, as illustrated on the chart below. Weiss (1983) concludes much of the difference can probably be attributed to selection bias.

	Gillam et al. (1976)	Brown et al. (1986)	McDonald et al. (1978)
Enumeration	unknown	Complete	100%
Latency	≥20 years	≥20	>20 years
Duration of exposure	≥5 years	≥5 - >30 years	>20 years
Observation period	13 years	37 years maximum	>20 years
Referent population	South Dakota	U.S. males	South Dakota
Observed/expected = SMR	7/2.2 = 3.2	27/25.5 = 1.06	7/5.6 = 1.24
p	<0.01	>0.05	>0.05
Source of records	1960 survey	Personnel records	Homestake Veterans Assoc. (1905 - 1973)

Bias resulting from incomplete enumeration can produce statistically significant but incorrect calculations of excess risk, greater than a 3-fold excess in this example of the Homestake miners cohort. Statistical significance becomes irrelevant in the presence of important biases and confounding of this magnitude.

D. Appropriate Referent Groups

It is important that the referent groups in an epidemiological study be as similar to the exposed group as possible (e.g., be from the same population with similar potential for exposure to other occupational carcinogens and similar lifestyle factors). Epidemiological studies are similar in construction to experimental studies but, unlike experimental studies, one has no control on the composition of the study population and little/no information regarding unmeasured risk factors such as diet, stress, health status, smoking. One can limit the effects of confounding from these important but unmeasured risk factors somewhat by using comparison groups from the same study population -- as in an internal cohort analysis or nested case-control study. In addition, as IARC (1997) points out, the credibility of a study is increased where "[i]nternal comparisons of disease frequency among individuals at different levels of exposure... have been made."

The study of British pottery workers by Cherry et al. (1995) is a good example of this. The authors found significantly increased SMRs for the workers when expected values were based on national rates (England and Wales); SMRs were reduced, in most cases to nonsignificance, when the expected values were based on local rates (Stoke-on-Trent). The authors then conducted two case-control studies using internal referents from the same study population and observed no association of lung cancer with silica. As these authors note, "evidence for an increase in risk of lung cancer...lies critically...in the choice of an appropriate [comparison] population (Cherry et al., 1995).

An important point to note, as discussed in Section II.F. below, is that there may be no appropriate referent group for compensated silicotics identified in registry studies.

E. Measure of Exposure-Response (E-R) Trends

Biological gradient is a major criterion in a weight-of-evidence review for assessing causality, because if exposure to the agent is causally related to lung cancer, the risk of lung cancer should be greatest in the highest exposed group. The best known and most commonly used metrics are cumulative exposure (intensity of exposure x length of exposure), or average exposure. Studies that have used either or both of these in a trend analysis are given the most weight in this Review. By contrast, a study that evaluates only point estimates of lung cancer risk using an external referent population without any attempt to assess E-R is considered a hypothesis-generating study. Such a study has limited sensitivity, and its value for testing the silica/lung cancer hypothesis is questionable.

Some studies use duration of exposure as a surrogate for cumulative exposure. Duration of exposure, however, generally is not an adequate surrogate for cumulative exposure because it rarely is the case that all jobs have similar concentrations over the time period covered by the study.

F. Silicotic Studies

Since 1980, there have been quite a few studies designed in whole or in part to consider the question whether silicotics have an increased risk of lung cancer -- or, put another way, whether silicosis is a risk factor for lung cancer. The vast majority of these studies are based on registries of compensated silicotics that contain no data on quantitative silica exposures, and present little, if any, information on smoking history or exposure to other potential occupational carcinogens.

The term "registry" in epidemiology is applied to all cases of a particular disease in a defined population such that the cases can be related to a population base (Last, 1983). For example, a cancer registry is one where all cancer cases are reported to a central registry. Another type of registry is not truly population-based but merely lists those persons known to or attending some agency that is providing them a service (e.g., blindness, drug addiction, high risk infants) or that determines the individual status of volunteers (e.g., silicosis or compensation registries). The silicosis type of registry usually comprises volunteers from an unknown population base and generally contains inadequate information on exposure to silica and other potential carcinogens.

As IARC (1987, 1997) and others have observed, silicotic registry studies generally suffer from a number of significant biases and potentially confounding factors that severely limit

their value in assessing whether silicosis *per se* is a risk factor for lung cancer. McDonald (1995) groups the shortcomings of registry studies under six headings:

1. Ascertainment

Registry studies tend to be characterized by potentially severe selection bias or incomplete ascertainment, because the identified silicotics are volunteers or self-selected applicants for compensation. In hospital-based studies, the selection bias may be even more pronounced, because persons with silicosis and lung cancer are more likely to be admitted to hospitals than persons with silicosis alone (IARC 1997). Among other things, the volunteer or self-selected nature of silicosis registries means that persons with smoking-related disabling symptoms (including possible incipient lung cancer) will be over-represented in the study population. As McDonald (1995) points out, those who seek and are granted compensation are unlikely to be representative of all silicotics. They are more likely to have social, psychological, and industry-related differences in addition to exhibiting more severe symptoms, radiographic changes, and lung function impairment. Moreover, even though it is not related to silica exposure *per se*, registered silicotics are more likely to suffer from airflow obstruction or other reduced lung function than referent populations. That in itself is an independent risk factor for lung cancer (Carta et al., 1991; Nomura et al., 1991; Kuller et al., 1990; Anthonisen et al., 1989; Tockman et al., 1987; Skillrud et al., 1986).

2. Confounding from Smoking

Registered silicotics are more likely to be smokers (and thus be at greater risk of lung cancer) than referent populations. This difference in smoking prevalence between registered silicotics and referent populations is an element of what IARC has referred to as the "noncomparability of referent subjects" (IARC 1987).

The high prevalence of smoking among registered silicotics means that smoking will generally be a major confounding factor in these studies. Heavy smokers are more likely to have respiratory impairment and other symptoms; consequently, for the same degree of fibrosis, they are more likely to seek and be granted compensation. For example, de Klerk and Musk (1998) noted in their cohort the strong association between lung cancer and smoking and between compensated silicosis and smoking. This suggested to them that smoking-related disabilities increase the likelihood of a successful claim for compensation. Therefore, they observed, results from studies of compensated silicotics "that ignored smoking may be questionable."

In addition to confounding the comparison to referent populations, the high prevalence of smoking among compensated silicotics means that registered silicotics may not be typical of other silicotics who do not exhibit smoking-related symptoms (and who, as a consequence, have not applied for compensation). As Partanen et al. (1994) note, patients who appear in the silicosis registries are likely to represent the more severe or advanced cases of silicosis.

3. Confounding from Occupational Exposures

Silicosis registries typically have very limited or incomplete information regarding exposures to other occupational carcinogens such as radon, PAHs, arsenic, nickel, and chromium. McDonald (1995) points out that these exposures may occur before or after silica exposure, thereby making it even more difficult to exclude the possibility of these exposures. The possibility of undocumented exposures to such agents may significantly confound the results of silicotic studies. Partanen et al. (1994), for example, estimated that asbestos exposures may have raised the RR in their study by 40 percent.

4. Diagnosis

Compensation boards often have to decide between various pneumoconioses in workers exposed to mixed dusts. And degree of disability frequently is more important than the kind of pneumoconiosis and the specific characteristics of the dust that caused it. Partanen et al. (1994) noted that misclassification of mixed dust pneumoconiosis as silicosis may have biased results in their study, but the extent of mixed dust pneumoconiosis in the Finnish silicotics and studies of other silicotics was not known. Moreover, prior to 1960, the radiographic categories did not differentiate between types of pneumoconiosis, so all pneumoconioses were lumped together.

Because of reader variability and other factors, there can be significant problems of misdiagnosis of radiographic silicosis, reflecting a lack of sensitivity (false negatives) or inadequate specificity (false positives or incorrect grading of silicosis severity). In registry-based studies, the identified silicotics may include a significant percentage of false positives (Amandus et al., 1992) -- particularly where aspects of chronic obstructive pulmonary disease or disability compensation are a major factor in the diagnosis.

An additional complication is that the diagnosis and compensability of silicosis have varied between countries and over different time periods. For example, as noted above, under some systems (e.g., Finland), mixed dust pneumoconiosis may be classified as silicosis for compensation purposes. In such cases, the actual relationship being investigated is between lung cancer and something broader than silicosis. These inter-country and inter-temporal differences in the diagnosis and compensability of silicosis also make it particularly problematic to conduct a "meta-analysis" of silicotic studies or to prepare a meaningful "scorecard" of results from the various studies.

5. Timing

In some proportion of cases, lung cancer may already be present when silicosis is diagnosed. Indeed, in some cases, lung cancer may have caused or contributed to the symptoms

or radiographic changes that resulted in discovery and diagnosis of silicosis leading to compensation. Failure to exclude even a small number of these individuals can produce an overestimate in the perceived risk (McDonald, 1995).

6. Expectation

The referent population is seldom adequate for a highly selected case series of compensated silicotics. The sick worker effect (the opposite of the healthy worker effect) will inevitably result in elevated risk ratios. Thus, there may be no appropriate referent group. There also is possible detection bias in these studies, because registered silicotics are examined more regularly than referent populations, thus increasing the likelihood that respiratory diseases of all sorts will be diagnosed among the silicotic group than among the controls.

* * * * *

In sum, registry-based studies of lung cancer risk among silicotics suffer from numerous biases and potential confounding factors. As IARC points out: "The existence and extent of these biases [and potential confounding factors] has seldom been evaluated in studies of silicosis and lung cancer" (IARC 1997). These biases and confounding factors, IARC observes, "make silicosis case registry-based case-control studies difficult to interpret" (IARC 1987). That is an understatement. In fact, the problem is more than simply difficulty of interpretation. The truth is that because they suffer from these biases, confounding factors, and an unknown level of misdiagnosis, registry-based studies are of very limited value in assessing whether silicosis increases the risk of lung cancer.

By contrast, nonregistry-based studies may be largely free of the biases and confounding factors that severely limit the usefulness of registry-based studies. A nonregistry study is that of a cohort design where a defined population is completely enumerated and workers are periodically examined to determine silicosis status. In such a study, the diagnosis of silicosis is more likely to be based on objective criteria that are determined independently and blindly and without consideration of symptoms or disability. An example of this is an analysis of lung cancer risk among silicotic workers that is nested within a larger cohort of silica-exposed workers. In such a study, enumeration and detection bias should be minimized, as essentially all employees are included in the cohort, and all are subject to the same surveillance and diagnostic procedures. In addition, such studies typically have much better information on potential occupational confounders than do registry-based studies. And, since the referent population is from the same occupational cohort as the silicotic subjects, the problem that IARC (1987) referred to as "noncomparability of referent subjects" (including potential differences in the prevalence of smoking) is mitigated.

For these reasons, studies of silicotics nested within a cohort of silica-exposed workers can provide a better test of the silicosis/lung cancer hypothesis than registry-based studies. Such studies, therefore, are emphasized in this Review. At the same time, however, we recognize that

if the diagnosis of silicosis in such a study is based on compensation, its usefulness for testing the silicosis/lung cancer hypothesis will be far more limited.

III. SELECTION OF STUDIES

The studies that meet all the requirements for inclusion in a weight-of-evidence review are listed in Tables 1 and 2 as Category One ("Studies that Meet the Criteria"). Also listed in Tables 1 and 2 are several studies that are relatively free of confounding from occupational carcinogens, and that therefore were considered by IARC to be important. However, these studies did not meet other criteria outlined in Section II of this Review. Accordingly, they are listed as Category Two ("Studies that Do Not Meet the Criteria"). The reasons for the Category One or Category Two listing are provided in the discussion of each individual study.

A. Category One: Studies that Meet the Criteria for Inclusion

1. Studies of Silica-Exposed Workers

a. Gold Miner Cohorts

Six cohorts of gold miners (four South African, one U.S., and one Australian) are considered to meet the criteria for selection discussed in Section II -- *viz.*, no apparent confounding from other carcinogens (with the possible exception of Hnizdo and Sluis-Cremer, 1991; Hnizdo et al., 1997), adequate control of smoking (with the exception of Steenland and Brown, 1995), quantitative estimates of exposure with examination of the E-R relationship, and adequate (internal) referent groups.

i) South African Gold Miners

The four cohorts of South African gold miners are the subject of studies by Hessel et al. (1986), Hessel et al. (1990), Hnizdo and Sluis-Cremer (1991), Hnizdo et al. (1997), and Reid and Sluis-Cremer (1996). The two studies by Hessel et al. (1986, 1990) are independent of each other; a few subjects could also be in Reid and Sluis-Cremer (1996). The two studies of Hnizdo (Hnizdo and Sluis-Cremer, 1991; Hnizdo et al., 1997) comprise the same cohort of gold miners and are a subset of Reid and Sluis-Cremer (1996). The worker population from which these study subjects are drawn is unique in that all miners are required to participate in a yearly medical examination that includes an x-ray. Current smoking has been recorded since 1960. For each worker, complete work histories including job, mine, and number of shifts are available. Estimates of exposure are similar in all studies and use the data of Beadle (1971) and/or Page-Shipp and Harris (1972) and include such metrics as shifts in high dust, total dusty shifts, average intensity, and cumulative dust exposure in units of particle-years or mg/m^3-years.

The two studies by Hessel et al. (1986, 1990) were both case control studies of white gold miners. The miners' pension fund for the years 1979-1983 was the source of the 133 lung cancer cases and 266 controls for the study by Hessel et al. (1986). (Approximately 85% of South African gold miners undergo autopsy examinations.) Matching was on year of birth and smoking. Hessel et al. (1990) matched 231 lung cancer cases with 316 controls by age at death. All cases and controls were selected from necropsy records, excluding miners who died between 1979-1983 so there was no overlap with Hessel et al. (1986). Also excluded were metastatic lung cancer cases, and miners with >1 year in asbestos mines, <1000 shifts in siliceous dusts, or >20% of time in nonsilica mines.

Average cigarettes/day were slightly higher in cases than controls at 5, 10, and 15 years prior to death in Hessel et al., (1986) and significantly higher (about 4 cigarettes/day) than controls at 5, 10, 15, and 20 years prior to death in Hessel et al. (1990). There were no significant differences in exposure between cases and controls in either study: Controls had slightly higher mean cumulative dust exposure, total dusty shifts, and shifts in high dust in Hessel et al. (1986). In Hessel et al. (1990), controls had slightly higher mean concentrations of cumulative dust exposure, total dusty shifts, and shifts underground. Calculation of ORs indicated no E-R trends, with all values equal to about one.

Neither study showed an association between lung cancer and silica exposure. These results are considered important and reliable for several reasons: (1) Smoking was collected on a regular basis and before disease occurred; (2) there was no association of lung cancer risk with years underground or dust exposure, suggesting the absence of confounding from radon; (3) there was no change in results when cases or controls who had silica-related diseases were removed from the analysis. It has been suggested that no E-R effect was seen in the Hessel et al. cohorts because of low exposure. This explanation seems unlikely, as there was a 33-fold range between highest and lowest cumulative exposure, and about 12 percent of cases and controls had moderate/pronounced parenchymal silicosis.

Hnizdo and Sluis-Cremer (1991) identified a cohort of 2209 white South African gold miners who participated in a study in 1968-1971 when they were 45-54 years old. To be selected the miners must have had 10 years underground work experience in gold mines with minimal work in other mines, and must have begun working in the period 1936-1943. Follow-up was through 1986. Smoking histories were obtained in the 1968-1971 survey. Silica exposure was based on average dust counts for occupational groups (Beadle, 1971). Using Cox's proportional hazard model, exposure-response trends for lung cancer and cumulative dust exposure (in respirable dust particle-year units) were analyzed for four time periods: to 1949, to 1959, to start of follow-up (1968-1971), and to end of follow-up (1986), as well as by actual years in mining. The 2132 non-lung cancer cases comprised the referents for the 77 lung cancer cases. Adjustments were made for age and smoking.

The most significant exposure metric for lung cancer risk was dust particle-years to start of follow-up, with a relative risk of 1.023 (1.005, 1.042)/1000 particle-years. The RR for men in the highest exposure category (>41,000 particle-years) relative to lowest exposure category (<15,000 particle- years) was 2.92 (1.02, 8.4). There was no association with years worked. There appeared to be a synergistic effect of smoking and silica exposure. The authors concluded that "the hypothesis that silica directly induces lung cancer cannot be rejected."

This study appears to meet all the criteria for inclusion. The lack of a trend with years underground but a trend with dust exposure suggests that radon was not a confounder. Selection bias is possible as the participation rate of eligible miners in the medical examination 1968-1971 was not provided, but participation is thought to be high.

Hnizdo et al. (1997) conducted a case-control study of the same cohort of gold miners reported on by Hnizdo and Sluis-Cremer (1991). The lung cancer cases are the same in the two studies. Five controls/case were matched on year of birth and survival of case. Chest radiographs were read by two experienced readers in the 1997 study, and a silicosis variable (category ≥ 1/1) was added to the analysis. The results of this case-control study (Hnizdo et al., 1997) are somewhat at odds with the case-cohort results (Hnizdo and Sluis-Cremer, 1991). In the 1997 study, silica exposure no longer is a significant variable when silicosis is in the model. The methods and results of the two studies are summarized in the chart below (which continues on to the following page)

	Hnizdo and Sluis-Cremer (1991)	Hnizdo et al. (1997)
Cohort	2209 white gold miners 45-54, 1968-1971.	2260 white gold miners 45-54, 1968-1972.
Design	Case-control (internal analysis) where controls are the rest of the cohort.	Case-control.
Lung cancer cases	77 (66 with necropsy).	78 (69 with necropsy).
Controls	2132 cohort members minus the lung cancer cases.	386 controls matched on year of birth and survival of case.
Dust exposure	11 job categories, (respirable dust counts) x (number of shifts), after Beadle (1971) expressed as particle-years.	9 job categories, (number dusty shifts) x (dust concentration) x (hrs underground)/270 x 8) expressed as mg/m^3; after Beadle (1971); dust levels from duToit (1991) and job categories from Page-Shipp and Harris (1972).

	Hnizdo and Sluis-Cremer (1991)	Hnizdo et al. (1997)	
Analysis	Cox proportional hazard model with best fit (log likelihood ratio) for 4 exposure variables , 4 smoking variables, and age at start of follow-up.	Conditional logistic regression adjusting for pack-years.	
Results	RR	OR	
		Silicosis not in Model	Adjusted for Silicosis
Pack-years	36: 8.91 (3.5, 22.7)	30: 10.1 (3.1, 33.6)	13.3 (3.1, 36.6)
High exposure group	2.92 (1.02, 8.4) (to start of follow-up; max lag 16 yrs)	3.19 (1.3, 7.6) (lagged 20 yrs)	1.93 (0.8, 5.0)
(≥20 years worked	1.58 (1.46, 1.71)	3.36 (1.02, 10.7) (lagged 20 yrs from death of case)	1.59 (0.5, 5.5)
Authors conclusions	Significant association of lung cancer with cumulative silica exposure and pack-years smoked.	No definitive interpretation possible: 1) only silicotics at risk, or 2) high silica exposure plus smoking causes lung cancer, and silicosis incidental, or 3) high silica exposure may be surrogate for radon exposure.	

Uranium production, a surrogate variable for radon, showed no significant association with the risk of lung cancer. Most of the deep mines had low radon levels, and knowledge of ventilation rates in the mines may "be required to detect an effect" of radon on lung cancer risk.

The results of Hnizdo and Sluis-Cremer (1991) and Hnizdo et al. (1997) are inconsistent with those of Hessel et al. (1986, 1990). Hnizdo et al. (1997) attempt to explain the discrepancy by suggesting that overmatching for dust exposure and silicosis may have occurred in the Hessel et al. (1986) study, where matching was based on year of birth and smoking, while Hnizdo et al. (1997) matched on year of birth alone.

Hnizdo et al. (1997) also suggest that deaths of miners with >15 years service are more likely to be reported than those with <15 years service, thereby producing overmatching on exposure and therefore on E-R trends. On the other hand, the only deaths that might not be reported are those with <15 years service who have been out of the mines for more than two years. Miners with >2 years service who claim their pension fund money will be reported. The

number of those not claiming their pension is not known, and there is no reason to suspect a difference in response rate of cases and controls. Hessel et al. (1986) suggest there is no overmatching on exposure as the average exposure (a time-independent measure) of cases and controls is similar.

Hnizdo et al. (1997) further note that in Hessel et al. (1986), cases and controls were matched on smoking, and they are therefore matched on premature deaths. That is, controls are likely to die prematurely from smoking-related deaths, and since silica exposure and smoking are risk factors for all cause mortality in gold miners, there may be overmatching on silicosis. The logic of this criticism is unclear, as it is not obvious that matching on smoking results in matching on silicosis.

Hnizdo et al. (1997) suggest that Hessel et al. (1990) is biased for two reasons. First, Hessel et al. (1990) matched cases and controls randomly by age at death. Hnizdo et al. (1997) observe that if the year of birth of controls and the year controls began working were later than for the cases, the controls would have had less duration of exposure prior to 1930 (when dust levels were high) than the cases. In that event, they say, the controls would have had lower cumulative exposure to silica than the cases even if the duration of exposure of cases and controls were comparable, because a greater proportion of the cases' exposure would have occurred prior to 1930 when silica levels were higher. But there is no difference with respect to cases and controls in average exposure, years underground, or shifts worked -- so year of birth and date of hire must have been essentially the same for cases and controls; thus, the differential in period of exposure between cases and controls suggested by Hnizdo et al. (1997) is unlikely.

Second, Hnizdo et al. (1997) state that miners awarded the highest degrees of compensation (*i.e.*, miners with pneumoconiosis and COPD) have fewer necropsies (65%) than others (85%). Therefore, in the Hessel et al. (1990) cases and controls, there will be under-representation of gold miners who have been significantly disabled in life (in part because of smoking) and who usually would have considerable exposure to silica. Hessel et al. (1990) discussed this problem, and suggest that because cases were not selected on the basis of smoking, the results are likely to be unaffected by the selection from necropsy records. In addition, the results are comparable to those of Hessel et al. (1986) where there probably was over-representation of fully compensated workers, thereby obviating this potential problem.

Reid and Sluis-Cremer (1996) conducted a nested case-control study of lung cancer in a cohort of 4925 white South African gold miners who were aged 39-54 in 1969 when they took their required annual medical examination. Vital status follow-up was through 1989. For the case-control portion of the study, only subjects were included who had spent at least 85% of their time working in gold mines and at least 15% underground. There were 159 lung cancer cases based on best available evidence. Two controls/case selected at random were matched on year of birth and must have survived the case. The purpose of this study was to assess the role of smoking and mining service on lung cancer, COPD, and ischemic heart disease (IHD). Exposure

metrics were years underground and cumulative dust exposure (mg/m^3-years), with exposure lagged 5 years (*i.e.*, exposures occurring 5 years before death were not counted). Cumulative exposure estimating procedures are similar to the other studies of South African gold miners.

A pack/day smoker was at 2.4-fold increased risk (1.4, 4.2) of lung cancer. After adjustment for smoking, there was no significant association of lung cancer and years underground, RR = 1.0 (0.78, 1.3) or cumulative exposure, RR = 1.2 (0.97, 1.3). The RR for the average miner exposed to 3.7 mg/m^3-years (27 years underground) was estimated at 1.52 (0.89, 2.64) ($p = 0.13$). The authors conclude that smoking was the main risk factor for lung cancer, and there was no significant association with dust exposure.

These studies from South Africa all appear to meet the criteria for inclusion in a weight-of-evidence review: All use internal referent groups; E-R analyses are adjusted for smoking; low levels of radon may be present, but, if present, are likely to have had only a small effect. There is overlap, *i.e*, some subjects are included in more than one study population as shown in the following listing. There is complete overlap of cases in the studies by Hnizdo (Hnizdo and Sluis-Cremer, 1991, Hnizdo et al., 1997), so they are not independent findings. This cohort appears to be largely a subset of Reid and Sluis-Cremer (1996), unless different mines were surveyed.

Hessel et al. (1986): 1979-1983; n = 133 lung cancer cases; from pension fund records.

Hessel et al. (1990): 1975-1979, 1983-1985; n = 231 cases; from necropsy database.

Hnizdo and Sluis-Cremer (1991); Hnizdo et al. (1997): 1970-1986; 78 lung cancer cases aged 45-54 in 1968-1972 survey.

Reid and Sluis-Cremer (1996): 1970-1990; 159 lung cancer cases aged 39-54 in 1969 survey.

The apparent association between lung cancer and particle-years of exposure in the study by Hnizdo and Sluis-Cremer (1991) is somewhat at odds with the results of the other South African gold miner studies. In this connection, it is instructive to note that the Hnizdo and Sluis-Cremer (1991) and Hnizdo et al. (1997) cohorts are a subset of the Reid and Sluis-Cremer (1996) cohort. Reid and Sluis-Cremer included twice the number of lung cancer cases because of the wider age range and longer follow-up and did not find a significant association with years underground or cumulative exposure after adjustment for smoking. Hnizdo et al. (1997) added the variable of silicosis, which reduced the association with dust exposure to nonsignificance; they conclude their results are not definitive and are open to various interpretations.

The most important South African gold miner studies are considered to be Hessel et al. (1986, 1990) and Reid and Sluis-Cremer (1996). The overlap in these studies is likely to be

small, and possible biases in ascertainment are different in each study as different sources were utilized in defining the cohort; yet, the results are consistent in showing no apparent association between lung cancer and silica exposure.

The IARC Working Group largely ignored the South African gold miner studies because there was concern that they might have been confounded by radon exposure. For this to be true, high dust exposure would have had to be correlated with low radon exposure. This supposition is highly unlikely. Years worked (or years underground) also has been used as a surrogate for radon exposure. The only study to show an association with years worked was Hnizdo and Sluis-Cremer (1991), suggestive of some possible radon confounding in that cohort. By contrast, there was no association between lung cancer and radon in Hnizdo et al. (1997).

The reasons for the differences between the findings in Hnizdo and Sluis-Cremer (1991) on the one hand, and Reid and Sluis-Cremer (1996) and Hnizdo et al. (1997) on the other are unclear particularly given the overlap in subjects and similar methods. Overall, however, the South African gold miner studies (including the studies by Hessel et al., 1986, 1990) fail to show an association between silica exposure and lung cancer. These data do not support the silica/lung cancer hypothesis.

ii) South Dakota Gold Miners

South Dakota gold miners were studied by Steenland and Brown (1995), McDonald et al. (1978), and Gillam et al. (1976). Steenland & Brown (1995) is a follow-up to Brown et al. (1986); accordingly, this latest follow-up is used for illustration purposes. The study by Gillam et al. (1976) comprised volunteers in a survey, and the participation rate was unknown. McDonald et al. (1978) studied workers with 21 years of service from this mine and used only years underground (UG) as the measure of exposure. The latest study by Steenland and Brown (1995) is a cohort of 3328 miners who had worked more than one-year underground between 1940-1965. The silica content of the respirable dust was 13% in 1970. Industrial hygiene measurements collected from 1937-1975 were above the TLV prior to 1950, and were used to estimate cumulative exposure (dust-years). Vital status was determined from 1977 to 1990 with 98% follow-up. There was a 3.5-fold excess risk of TB and a 2.6-fold excess of pneumoconiosis and other respiratory diseases, so silica exposure clearly was substantial.

There were 115 lung cancer deaths, with an SMR of 1.27 (1.02, 1.55) for those with >30 years since first exposure when county rates were used as the referent. There was no association of cumulative dust exposure and lung cancer by SMR analysis or in a nested case-control analysis stratifying by tenure, year of first exposure, and year of birth. Measured radon and arsenic levels were below Federal standards, and since there was no silica/lung cancer association, it is highly unlikely that arsenic and radon were confounders. Smoking histories were not available on the entire cohort, but since negative confounding from smoking is unlikely,

this study is considered not to be confounded by smoking. IARC (1997) also concluded that this study is not confounded and that it does not support the silica/lung cancer hypothesis.

iii) Australian Gold Miners

The most recent study of gold miners is from Australia (de Klerk and Musk, 1998). Because of its publication date, this study was not considered by IARC. In addition to the cohort analysis, it also includes a nested case-control study of miners evaluating E-R trends. The cohort comprised 2297 goldminers examined in 1961, 1974, and 1975 with follow up through 1993. Participation rate was thought to be about 95%, with vital status determined on 89% of the cohort, more than half of whom had died. Eighty-four percent of the cohort had smoked at some time. There is no apparent confounding from arsenic or radon in the study, adjustment for smoking appears adequate, and there are semiquantitative estimates of cumulative exposure and intensity of exposure (or average exposure). The SMRs for lung cancer were 1.26 (assuming subjects lost to follow-up were alive at the end of 1993), and 1.49 assuming person-years stop at date the person is last known to be alive. The SMRs for pneumoconiosis under these alternative assumptions were 9.5 and 11.2, respectively.

The 138 lung cancer cases were matched on age with 631 controls known to be alive at time of lung cancer diagnosis. One case was a nonsmoker, and smokers of >25 cigarettes/day were at about a 50-fold increased risk of lung cancer. E-R trends were evaluated using cumulative exposure (exposure-score years, and log exposure-score years), log of duration of surface and underground exposure, and intensity of underground and surface exposure.

Risk ratios were nonsignificant and around one after adjustments for smoking and bronchitis in one analysis, and after adjustments for smoking, bronchitis and silicosis in another analysis. The one significant association was with log (exposure-score year) after adjustment for smoking and bronchitis. Whether log cumulative exposure is a better measure than cumulative exposure was not determined as no *a priori* objective method for judging the best model was applied to these data. Cumulative exposure is considered the more appropriate exposure metric, and is the most commonly used metric. The authors conclude there was no evidence that exposure to silica caused lung cancer in the absence of silicosis.

b. Chinese Workers

McLaughlin et al. (1992) studied Chinese workers in four separate nested case-control analyses of tin miners, tungsten miners, iron-copper miners, and pottery workers. The cohort was comprised of males employed 1972-1974, with follow-up to 1990 (Chen et al., 1992). Four controls/case were individually matched on decade of birth and mine or factory of employment. The cumulative respirable silica exposure matrix was externally validated by increasing OR for silicosis for each succeeding exposure category. Exposures to silica were unusually high as mean total dust level estimates ranged from 28 mg/m^3 (1950) to 3 mg/m^3 (1988), with a mean of

9 mg/m^3 for all years (Dosemeci et al., 1993). The high silica exposures are reflected in the high SMRs for pneumoconiosis in the cohort study: a 50-fold increase in the tungsten miners, a 16-fold increase in iron-copper miners, and a 30-fold increase in the pottery workers (Chen et al., 1992). The number of lung cancer cases in the case-control studies was 93, 174, and 62, respectively.

Measurements for radon, arsenic, and PAHs were available since 1980. Smoking history was obtained by questionnaire administered to study subject or next of kin. Quantitative estimates of exposure to dust, silica, arsenic, radon, PAHs, and smoking histories were available for all segments of the study, and adjustments were made for smoking in the E-R analyses. The study of tin miners clearly was confounded by arsenic and was considered unsuitable for testing the silica/lung cancer hypothesis. The tungsten and iron-copper miner studies showed no positive or significant ($p > 0.05$) independent associations with arsenic, radon, or PAH -- so potential exposures to those substances are unlikely to confound a potential association with silica. In the iron-copper mine study, the E-R trend with silica exposure was not significant ($p > 0.05$). In the tungsten miner study, the E-R trend with silica exposure was significant ($p < 0.01$), showing a decreasing risk of lung cancer as silica exposure increased.

The pottery workers in this cohort show a nonsignificant trend for the risk of lung cancer to increase as PAH exposure increased, with an OR of 1.7 in the highest PAH exposure category. There is the suggestion of an association ($p > 0.05$) with cumulative respirable silica exposure; the highest risks were in the low (OR = 1.8) and high (OR = 2.1) silica exposure categories. PAH and silica concentrations were correlated in the potteries ($r = 0.56$) thereby hindering evaluation of their separate effects. When adjustment was made for PAHs in the silica E-R analysis, the ORs were raised rather than lowered. This anomalous effect was not clarified by the authors, but could be due to several factors such as better exposure estimates for silica than for PAHs, interaction of PAH and silica that was not tested for in the analysis, and a poor fitting model because of nonlinearity. The high temperature needed for firing pottery may result in possible exposure to cristobalite.

These studies are among the few with historical records of past workplace concentrations for both silica and potential confounders. Silica exposures appeared to be quite high, as was smoking prevalence (93% among cases and 80% among controls). However, the risk of lung cancer for 20-cigarette/day smokers was not very high; 7.4-fold in potteries, 7.3-fold in iron-copper mines, and 3.9-fold in tungsten mines. Whether the method of collecting smoking history from next of kin resulted in recall bias, particularly for lung cancer cases, cannot be determined.

IARC (1997) noted that the study of tungsten miners is one of the "noteworthy instances where a relationship between lung cancer and crystalline silica was not detected" and where confounders were taken into account. The tungsten miner study population had the largest number of cases and controls -- with a high proportion of cases in the high exposure group. This

study is among the most noteworthy of the groups studied by McLaughlin et al. (1992) and should be given the greatest weight.

In the iron-copper miner cohort studied by McLaughlin et al. (1992), there was no E-R trend: The risk of lung cancer was 1.3 in the middle exposure groups but reduced in the high exposure group. About 20% of the cases and 11% of controls had radiological silicosis. Confounding from arsenic is unlikely, as there were no cases or controls with medium or high exposure to arsenic, and the OR was <1.0 for the few cases in the low exposure group. The exposure to PAH began recently (early 1980s), so there was inadequate latency for PAHs to contribute to the risk of lung cancer. If PAH and radon are confounders, the most likely effect would occur in the high silica-exposed group. However, in the silica E-R analysis, the highest exposure group had the lowest OR. Thus, there should be no confounding from PAHs or radon in this study. In that respect, this study is similar to the study of tungsten miners, and less confounded than the study of pottery workers.

The studies of tungsten and iron-copper miners do not support the silica/lung cancer hypothesis. The pottery worker study provides some support, but it is difficult to disentangle the confounding effects of occupational carcinogens.

c. U.K. Pottery Workers

There are a series of reports on British pottery workers. Cherry et al. (1995) found significantly increased SMRs for U.K. pottery workers when expected values were based on national rates (England and Wales); SMRs were reduced, in most cases to nonsignificance, when the expected values were based on local rates (Stoke-on-Trent). They therefore conducted two case-control studies using internal referents from the same study population and observed no association of lung cancer with silica. In summarizing the results of the 1995 study, the authors note that "evidence for an increase in risk of lung cancer...lies critically...in the choice of an appropriate [comparison] population." (Cherry et al., 1995).

Only the last study in this U.K. pottery worker series (Cherry et al., 1997) meets the exposure criterion for consideration in a weight-of-evidence review. Analysis was restricted to 52 lung cancer cases without exposure to asbestos or foundry work and >10 years latency. Three or four referents/case were matched on date of birth and date of first exposure. Since all cases were smokers, only referents who had ever smoked were included. Smoking information had been collected every two years since 1950, although history was missing for about 25% of cases and referents. Seventy percent of cases and 47% of referents were heavy smokers (20 cigarettes/day). A job exposure matrix was constructed from 1300 air samples collected since 1930. Both cumulative and average intensity of exposure were strongly associated with radiographic opacities of 1/0 or greater. (Burgess et al., 1997).

Among workers with ≥10 years latency and with adjustment for smoking and radiographic evidence of silicosis, there was a nonsignificant negative E-R association between lung cancer and cumulative exposure to silica (adjusted OR = 0.60, 90% CI = 0.26,1.41) and a nonsignificant positive trend between lung cancer and adjusted average exposure (OR = 1.68, 90% CI = 0.93, 3.03). An increasing risk of lung cancer was associated with ever working in a job with exposure >400 $\mu g/m^3$ (OR = 2.07, 90% CI = 1.04, 4.4). This association disappeared when adjustment was made for ever working in firing or post-firing jobs, where the authors speculate that conversion to cristobalite may occur. The OR was 2.17 (90% CI = 1.16, 4.07) for ever working in a firing or post-firing occupation compared to never working in such a job.

The role of chance may be important in this study, one of the smaller ones in terms of number of deaths and the only one to use 90% confidence intervals. Cherry et al. (1997) showed within 90% confidence limits that the risk of lung cancer among pottery workers exposed to >4000 $\mu g/m^3$-years quartz lies between 0.26 and 1.41, and is not significantly different from the risk among workers in the group having <4000 $\mu g/m^3$-years exposure to quartz. They also showed within 90% confidence limits that workers ever exposed in firing or post-firing jobs where conversion to cristobalite may occur had a risk of lung cancer between 1.16 and 4.07. Because a 90% confidence interval was used, the increased risk of lung cancer associated with employment in firing or post-firing jobs (where exposure to cristobalite may have occurred) has something more than 1 chance in 10 of being a random occurrence ($p < 0.10$). The absence of an association between lung cancer and cumulative quartz exposure in this study clearly is not the result of chance, while the positive association with firing or post-firing employment might be a chance occurrence.

The authors conclude that the only risk factor identified in this study of U.K. pottery workers was employment in firing or post-firing jobs, and they suggest that cristobalite might be the relevant exposure in those jobs. However, cristobalite air concentrations were not measured, and potteries attempt to minimize conversion to cristobalite because it reduces the quality of the finished product (although 8% cristobalite was measured in pottery samples). Consequently, the extent to which the increased lung cancer rate in firing or post-firing employment was attributable to cristobalite remains speculative; moreover, the possibility of a chance occurrence cannot be discounted, as the use of 90% confidence intervals indicates only marginally significant results. Thus, this study lends weak support to a possible association of lung cancer with cristobalite exposure, but it does not support the silica/lung cancer hypothesis where exposure is to quartz.

d. Iron Foundry Workers

Andjelkovich et al. (1994, 1992, 1990) reported on a cohort of 8,147 iron foundry workers employed for at least 6 months from 1950 - 1979, with follow-up through 1984. The cohort study showed SMRs of 1.23 (0.96, 1.54) for lung cancer among white males and 1.32 (1.02, 1.67) among nonwhite males that were largely attributed to smoking. SMRs showed a

nonsignificant inverse trend with years worked among those with >20 years since first employment (Andjelkovich et al., 1990).

The nested case-control study (Andjelkovich et al., 1994) added 5 years follow-up and 72 lung cancer cases for a total of 220 and assessed E-R trends for formaldehyde, cumulative silica exposure, and smoking status. Controls were matched on race and attained age of the case. A smoking survey was conducted of all cases and 2 controls/case among study subjects or next of kin. Histories were obtained on about 70%. About 92% of cases and 67% of controls had ever smoked; there was a RR of about 5 for known eversmokers compared to known nonsmokers.

An E-R analysis using 10 controls/case (smoking adjustments by year of birth) and 2 controls/case (adjusted for smoking by ever vs. never smoking) showed similar results, namely, there was no evidence that silica or formaldehyde contributed to an excess lung cancer, as the OR in the 4th exposure quartile ranged from 0.90 to 1.26 (2 controls/case) and 0.65 to 1.18 (10 controls/case) for lag periods of 0, 10, 15, and 20 years. There was no association of increased lung cancer risk by years worked in work areas, including core making, where almost all formaldehyde exposures occurred, and molding where the highest exposure to silica and PAHs occurred.

Smoking was a strong predictor of mortality but not a confounder based on similarity of results between 2 controls/case with smoking data and 10 controls/case with no individual-level smoking data but with matching on birth date as an indirect adjustment for smoking. The authors also considered that formaldehyde was unlikely to be a confounder as the percentage exposed (~25%) was too small to detect a lung cancer risk; in addition, there was no E-R trend. Benzo(a)pyrene [B(a)P] levels were low and so was not a confounder as in other foundry studies where coal tar pitch was used as an additive rather than coal powder. Coal tar pitch use in many foundries may increase B(a)P exposure 50-fold. Lag periods up to 20 years were considered, thereby eliminating "from consideration foundry exposures that may not have had sufficient latency to be of etiologic importance." However, calculations suggest that approximately 90% of deaths had adequate latency. The lack of a difference in effect by lag period, along with the lack of association with silica exposure, detracts from the silica/lung cancer hypothesis. IARC also noted the lack of an E-R trend, but did not specifically address confounding except to note the presence of a variety of air pollutants at this foundry. There was exposure to potential respiratory irritants such as acrolein, bentonite clay, formaldehyde, and ammonia. The authors did not consider these pollutants to be confounders. Formaldehyde is considered a potential lung carcinogen, but was not considered a confounder as there were no excess risks in the work areas where these substances were in highest concentrations, and separate analyses showed no association of lung cancer and formaldehyde.

Andjelkovich et al. (1995) analyzed a subset of the foundry cohort to assess the effects of formaldehyde exposure on mortality. The subset of men exposed to formaldehyde for the years between 1960 and 1987 consisted of 48% of the foundry cohort. An SMR analysis showed few

differences in mortality (including lung cancer) between the formaldehyde-exposed cohort and an internal population who had worked in the foundry over the same time period but were not exposed to formaldehyde. An internal analysis using the unexposed population as the referents showed no association between formaldehyde exposure and malignant or nonmalignant diseases of the respiratory system. Ever smokers compared to never smokers had a 2.1-fold increased risk of lung cancer and a 6.93-fold increased risk of diseases of the respiratory system. There were E-R trends for silica (but not formaldehyde) associated with the risk of both lung cancer and diseases of the respiratory system. Lung cancer risk ratios were 2.34 (0.68, 10.7), 3.41 (1.16, 14.5), and 3.98 (1.41, 16.6) when comparing second, third, and fourth quartiles to the first quartile silica exposure group.

The association of lung cancer and silica exposure found in Andjelkovic et al. (1995) is in sharp contrast to the lack of any such association in the full cohort study (Andjelkovic et al., 1994). For several reasons, the nested case-control study (Andjelkovic et al., 1994) is considered the more appropriate study to use in weighing the evidence of an association between silica exposure and lung cancer.

- The purpose of the first case-control study (Andjelkovic et al., 1994) was to assess the potential association of silica and formaldehyde with lung cancer. The purpose of the second study (Andjelkovic et al., 1995) was to assess the association of formaldehyde with mortality. The lung cancer/silica finding in the second study was an incidental finding, whereas the first study attempted to directly test the silica/lung cancer hypothesis.

- The first case-control study had more cases (220 vs. 51), more information on smoking (76% in cases and 69% in controls compared to 65% of exposed vs. 55% of unexposed), and 10 more years follow-up (1950-1989 vs. 1960-1989) than the second formaldehyde study.

- The first case-control study reflects more extensive data collection to gather smoking data and more analyses (such as analysis by four different lag periods with both 2 and 10 controls/case, as well as by work area).

The authors (Andjelkovic et al., 1995) suggest overmatching may have reduced the differences in silica exposure between cases and controls in the first case-control study. This is unlikely as there were only two matching criteria: race and attained age of case. The difference in results may be due to the distribution of silica exposure. It would be useful to use the same absolute exposure categories in the two studies to help determine whether distribution of exposure could explain such a big difference in results.

In sum, the lung cancer case-control study (Andjelkovic et al., 1994) is considered the more relevant study. IARC apparently reached the same conclusion, as no reference is made to

Andjelkovic et al. (1995) in the IARC (1997) Monograph. The lung cancer case-control study (Andjelkovic et al., 1994) also appears to satisfy the criteria for inclusion in a weight-of-evidence review, and it does not support the silica/lung cancer hypothesis.

e. Diatomaceous Earth Workers

IARC (1997) considered Checkoway et al. (1996) to be one of the most important of the silica studies. The 1996 study is a reanalysis of an earlier report (Checkoway et al., 1993). It was limited to 2266 men who were employed at least one day between 1942-1987 and who had attained more than one-year of cumulative service. Based on the evaluations of asbestos exposure by Gibbs and Christensen (1994), all jobs were assigned an asbestos exposure level. However, workers hired prior to 1930 were excluded from the cohort because, while asbestos was used prior to 1930, exposure levels could not be determined (Checkoway et al., 1996). The chrysotile asbestos used at the plant was micropulverized, a process similar to that used in asbestos textile plants where lung cancer risks are among the highest reported for any asbestos-exposed group. During the pre-1930 period, there also was no flux calcining. Flynn, Rosol, and Kinsala (1991) report that at temperatures up to 800°C for three days, no detectable cristobalite is formed without flux.

Subsequent to analysis of the 1996 cohort (Checkoway et al., 1996), there was an additional seven years of follow-up to 1994. Most of our attention will be focused on this follow-up study (Checkoway et al., 1997). There are some differences between the 1996 and 1997 studies. The workers hired prior to 1930 were excluded by Checkoway et al. (1996) because asbestos exposure could not be assessed; they were included in the follow-up study (Checkoway, 1997). Also, for the follow-up study, additional exposure data for silica were found going back to 1948, and silica exposure categories were expressed in mg/m^3-years instead of mppcf-years. Exposures in the pre-1930 years were based on extrapolation from estimates of 1930 concentrations (Checkoway et al., 1997). This is significant because asbestos was not used in 1930, but was used prior to 1930. As a result, asbestos exposures for the pre-1930 years are underestimated in Checkoway et al. (1997). Conversely, flux calcining was used in 1930, but was not used prior to 1930. As a result, exposures to cristobalite are likely to be overestimated for the pre-1930 years since they are based on estimates of cristobalite exposure in 1930. Thus, the pre-1930 hires may be assigned an inappropriately low asbestos exposure category and an inappropriately high crystalline silica exposure category -- thereby producing an underestimate of asbestos-related risk and an overestimate of silica-related risk.

Without considering asbestos exposure, the SMRs for lung cancer by decade of hire from <1920 to 1960 - 1969 were 20.8, 1.5, 1.3, 1.3, 1.3 and 0.7. A significantly increased RR of 2.15 for lung cancer with 15-year lag was observed in the high silica exposure category. Internal Poisson regression analyses were conducted to evaluate E-R trends of lung cancer mortality with respirable silica exposure. Separate analyses were conducted -- one without adjusting for asbestos and one adjusting for asbestos exposure. The E-R trend was the same either with or

without adjustment for asbestos. Because of the lack of influence of asbestos on the E-R trends, the authors considered that asbestos was not a confounder. Other evidence cited in support of this view was that there was no independent risk of lung cancer from asbestos, and only one death each from mesothelioma and asbestosis.

Internal analyses provided relative risk (RR) estimates for lung cancer by cumulative exposure to cristobalite and asbestos. The results are shown in the table below. For the highest silica exposure category, there is about a 2-fold excess risk for lung cancer in the various asbestos exposure categories; none of these risks is statistically significant.

Lung Cancer RR (internal analyses) by Silica and Asbestos Exposure Lagged 15 Years (adjusted for age, calendar year, duration of follow-up, and ethnicity)

Silica Exposure (mg/m^3 x years)	Asbestos Exposure (f/ml x years) 0	0 - 1.20	≥1.20
<0.5	1.0	0.88 (0.25, 3.14)	0.57 (0.07, 4.46)
0.5 - 1.1	0.73 (0.26, 2.01)	1.27 (0.42, 3.86)	0.93 (0.26, 3.28)
≥1.1 - <2.1	0.73 (0.26, 2.03)	1.19 (0.34, 4.16)	0.33 (0.04, 2.53)
≥2.1 - <5.0	1.0 (0.38, 2.62)	0.75 (0.17, 3.32)	1.90 (0.71, 5.05)
≥5.0	2.03 (0.93, 4.45)	2.09 (0.68, 6.47)	1.77 (0.50, 6.22)

Checkoway et al. (1997) conclude "our dose-response analysis provides support for the hypothesis that crystalline silica is a human lung carcinogen albeit not an overwhelmingly potent carcinogen."

When analyzed by date of hire, the only significant lung cancer excess occurs in those hired prior to 1930 (SMR = 2.33 with 8 observed deaths). The E-R results by both silica and asbestos exposure as shown above indicate no statistically significant excess in any exposure category, although the RRs are doubled in the highest silica exposure categories. In the other exposure categories, the RRs are around the null value. Exposure misclassification is probable, as most if not all of the pre-1930 hires are likely to be placed by Checkoway et al. (1997) in the high silica exposure and lower asbestos exposure categories, as silica exposures were thought to increase as one goes back in time. At least some of the pre-1930 hires, however, probably should be placed in a low-silica, high-asbestos exposure category. Thus, the risk of lung cancer is probably overestimated in what Checkoway et al. (1997) describe as the high-silica, low-asbestos categories. Because of misclassification, at least some of the increased risk in these categories

should be attributed to asbestos, and some of the risk attributed to cristobalite should be discounted.

Checkoway et al. (1997) comment that the validity of the E-R analyses is "largely dependent on the quality and completeness of exposure data." Sources of measurement error in addition to those discussed above include: a) uncertainty in extrapolation backward to the years before 1948; b) uncertainty in conversion of a mppcf metric to gravimetric estimates of respirable silica; c) uncertainties in relative amounts of crystalline silica in the dust; d) uncertainties in asbestos exposure levels which were based on two small dust-mixing operations 1952-1977; and e) uncertainties as to which workers were exposed to asbestos. "Therefore, misclassification of asbestos exposure may have hindered our ability to control for asbestos as a potential confounder."

In addition to asbestos, smoking also is a possible confounder in this study, as smoking prevalence was correlated with exposure. Based on smoking data for 50% of the cohort, prevalence was 64% in the lowest silica exposure category and 84% in the highest (Checkoway et al., 1997). Even though the referent group is not inappropriate, confounding from cigarette smoking may still bias away from the null the estimated risk of lung cancer in the high silica exposure categories. Using the Axelson (1978) method for indirect adjustment of smoking and a RR of 20 for smokers vs. nonsmokers, about 29% of the RR is attributable to smoking. Subtracting this estimated effect of smoking from the highest RR (2.15 in the $\geq$18.3 mg/m^3-year exposure category) gives a nonsignificant RR of 1.86 with a lower CI of 0.79. In the zero asbestos exposed group, the adjusted RR becomes 1.74, with a lower confidence interval of 0.64.

In sum, this study appears to be confounded by asbestos and cigarette smoking, and biased by misclassification of asbestos and silica exposure. Checkoway et al. (1997) disagree that asbestos and smoking can explain the association. But even without consideration of bias and confounding and considering E-R in the silica/asbestos exposure matrix, the excess risks in the high exposure categories could be a chance occurrence.

These results (Checkoway et al., 1997) are included among the studies that meet the criteria for a weight-of-evidence review. However, at a minimum, this study should be given a low weighting for the reasons noted above.

f. Summary

The foregoing studies of silica-exposed workers are considered appropriate for testing the silica/lung cancer hypothesis, as they meet most of the criteria set out in Section II. Most include case-control studies nested within completely enumerated cohorts. Thus, the referent populations are appropriate as they are from the same population as the cases and, except for disease status, should be roughly comparable to the cases for important unmeasured risk factors such as diet, social and economic status, etc. Exposure to occupational carcinogens generally

appears to be minimal -- as judged by low exposure levels, separate E-R analysis by carcinogen, or lack of trend with increasing years worked or silica exposure. Latency was generally not taken into account, but this probably does not bias the results, as most subjects appeared to have had adequate time since first exposure to develop silicosis and lung cancer. Most of these studies made direct adjustment for smoking (except Steenland and Brown, 1995; and Checkoway et al., 1997).

A possible exception with respect to meeting these criteria is the study of diatomaceous earth workers. The limited smoking data suggest smoking prevalence was higher in the high silica-exposed workers compared to low silica-exposed workers. Also, there is likely confounding from asbestos exposures and misclassification of silica exposure in the pre-1930 hires, the only group that clearly is at increased risk of lung cancer.

In these studies, there is a generally a consistent pattern of no silica/lung cancer E-R trends, with some suggestions of marginally increasing trends (Reid and Sluis-Cremer, 1996; Hnizdo and Sluis-Cremer, 1991; Hnizdo et al., 1997; McLaughlin et al., 1992) (Figure 1).

Two of the studies investigated a possible association of lung cancer with exposure (Checkoway et al., 1997, 1996) or presumed exposure (Cherry, et al., 1997) to cristobalite. The significance of the study of U.K. pottery workers by Cherry, et al (1997) remains uncertain because the presumed cristobalite exposures are undocumented, there is no E-R analysis, and the increased lung cancer risk among workers ever employed in firing or post-firing jobs could be a chance occurrence. The study by Checkoway et al. (1997, 1996) of diatomaceous earth workers shows a statistically significant increased risk in the highest exposed group only when workers with potential asbestos exposure before 1930 are included in the analysis. When those workers are excluded from the analysis, the power of the study is reduced, and there is no significantly increased risk of lung cancer even in the group of workers with highest silica exposure. Moreover, pre-1930 cristobalite exposure was likely to be low, since flux calcining was not used at that time. In sum, smoking and misclassification of cristobalite and asbestos exposure are alternative hypotheses for the increased risk of lung cancer seen in the study by Checkoway et al. (1997, 1996).

2. Silicotic Studies

Several studies of silica-exposed workers also have evaluated the silicosis/lung cancer hypothesis. Most of these studies that are included in Category One appear to have avoided enumeration and diagnosis bias (*i.e.*, compensation-based diagnosis). The studies of silica-exposed workers discussed in Section III.A.1. above that also test the silicosis/lung cancer hypothesis and remain in Category One for that purpose are Hessel et al. (1986, 1990); Hnizdo and Sluis-Cremer (1991); Hnizdo et al. (1997); Cherry et al. (1997); and, somewhat less clearly, McLaughlin et al. (1992). Several other studies providing analyses by silicosis status also

qualify for inclusion in Category One. These are Carta et al. (1991) and, somewhat less clearly, Dong et al. (1995). These silicotic studies are discussed below by type of exposure.

Three types of analyses have been conducted and are summarized in Figures 2 and 3. They are: a) silicotics versus nonsilicotics, b) silicosis by severity of diagnosis, and c) silicosis by dust exposure. If silicosis is a risk factor for lung cancer, then one would predict: a) the risk will be higher for silicotics compared to nonsilicotics (in the absence of bias and after adjustment for age and smoking); b) the risk for lung cancer will increase as severity of silicosis increases; and c) silicotics in higher silica exposure categories will be at increased risk compared to silicotics with lower cumulative silica exposures.

a. South African Gold Miners

There are two South African gold miner studies utilizing autopsy diagnosis of silicosis (Hessel et al., 1990; Hnizdo and Sluis-Cremer, 1991), one using radiological diagnosis (Hnizdo et al., 1997), and one using both (Hessel et al., 1986). As discussed in Section III.A.1. above, these studies meet the criteria for testing the silica/lung cancer hypothesis. Since the diagnosis of silicosis in these studies does not appear to be based on compensation criteria, and since enumeration is nearly complete and selection bias is not a problem, they also meet the criteria for inclusion in testing the silicosis/lung cancer hypothesis.

Autopsy diagnoses are regularly conducted at the National Center for Occupational Health by pathologists with knowledge of occupational history and well before the subjects are included in any of the epidemiological studies. Each miner in South Africa is graded for silicosis of the parenchyma, pleural, and hilar glands on macroscopic examination. The diagnosis is then confirmed by histological examination of tissues from the upper, middle, and lower zones of both lungs and hilar glands (Hessel et al., 1986, 1990; Hnizdo and Sluis-Cremer, 1991). Since histological silicotic lesions are unique in appearance, the diagnosis is considered reliable and a specific marker for silica exposure. Parenchymal and, to a lesser extent, pleural silicotic lesions are considered dose-related measures of response. Hilar gland silicosis may be a measure of exposure, but hilar gland silicosis is not necessarily correlated with level of exposure, and about 80-90% of exposed workers have it. Thus, hilar gland silicosis will not be considered important in testing the silicosis/lung cancer hypothesis.

Based on autopsy diagnoses, Hessel et al. (1986) found no increased risk of lung cancer for silicotics compared to nonsilicotics for parenchymal silicosis (OR = 1.49; 0.94, 2.34; p = 0.11) or pleural silicosis (OR = 0.72; 0.42, 1.24; p = 0.30 (Figure 2). There was a nonsignificant (p = 0.08) but suggestive trend for the risk of lung cancer to increase with increasing severity of parenchymal silicosis. There was no trend with increasing severity of pleural silicosis (p = 0.30). For all categories of parenchymal silicosis, there was no trend for the odds of lung cancer to increase with increasing cumulative exposure to dust (p >0.05) (Figure 3).

Hessel et al. (1986) also had two experienced readers independently -- and without knowledge of case-control status, silica exposures, or smoking history -- read chest x-rays taken ≥3 years prior to death. The risk of lung cancer was not increased among the radiologically diagnosed silicotics compared to nonsilicotics (OR = 1.08, 0.63, 1.82, p = 0.92) (Figure 2).

Hessel et al. (1990) conducted a similar analysis among gold miners identified from necropsy records. The lung cancer OR for parenchymal silicotics compared to nonsilicotics was 1.10 (0.79, 1.60), while the OR for pleural silicotics compared to nonsilicotics was 0.80 (0.54, 1.20) (Figure 2). There was no trend for lung cancer risk to increase with increasing severity of parenchymal silicosis (negative trend, p = 0.76), or pleural silicosis (negative trend, p = 0.09) compared to nonsilicotics. Another analysis assessed lung cancer risk by quartiles of dust exposure among workers with parenchymal and pleural silicosis compared to nonsilicotics, but without regard to severity. This analysis showed no E-R trends for lung cancer risk to increase with increasing levels of cumulative dust exposure for either parenchymal silicosis (overall OR = 1.10, 95% CI = 0.77, 1.58; p >0.20) or pleural silicosis (OR = 0.79, 95% CI = 0.52, 1.19; p = 0.20). Separate ORs for silicotics and nonsilicotics by quartiles of cumulative dust exposure were calculated from the data and showed no E-R trends for either category (Figure 3). This study provides no support for the hypothesis that silicotics are a susceptible subpopulation for lung cancer. To the contrary, the lack of a dose-response relationship with increasing severity of silicosis and the absence of an E-R trend with increasing dust exposure for either silicotics or nonsilicotics provide strong evidence against both the silica/lung cancer hypothesis and the silicosis/lung cancer hypothesis.

Using autopsy diagnoses, Hnizdo and Sluis-Cremer (1991) found no association between lung cancer and parenchymal silicosis (OR = 0.9) or pleural silicosis (OR = 1.2) compared to nonsilicotics after adjustment for age at death, dust particle-years, and smoking (Figure 2). The authors did find an association between hilar gland silicosis and lung cancer, with a trend for lung cancer risk to increase with increasing severity of hilar gland silicosis. The reason for the differences between hilar gland silicosis and parenchymal/pleural silicosis is not obvious; however, as noted above, parenchymal and pleural silicosis are considered to be more important than hilar gland silicosis in testing the silicosis/lung cancer hypothesis. Smoking was not correlated with silicosis in this study, and the correlation of silicosis with dust years was not reported. These data do not support the silicosis/lung cancer hypothesis.

Hnizdo et al. (1997) had radiographs of cases and controls read in chronological order by two experienced readers to separate silicotics (≥1/1) from nonsilicotics in the same cohort as Hnizdo and Sluis-Cremer (1991). X-rays taken three or fewer years before death were not read. Seven lung cancer cases and 41 controls were lost to follow-up. After adjustment for smoking, the odds of lung cancer were increased 2.45-fold (95% CI = 1.2, 5.2) among the silicotics. After adjustment for both smoking and cumulative exposure to silica (lagged 20 years), the OR for lung cancer was increased 2.1-fold but was no longer significant (95% CI = 1.0, 4.6). Lung cancer cases with radiological silicosis (category ≥1/1) had more years worked, more smoking

pack-years, and significantly greater dust exposure than the lung cancer cases without silicosis. There were no differences in exposure or years worked between nonsilicotic cases and controls, but nonsilicotic cases still smoked more than controls. Smoking was not associated with the risk of silicosis or age at onset of silicosis, but smoking and silicosis multiplied the risk of lung cancer, as shown by the 4-fold increased risk of lung cancer comparing light and heavy smokers with and without silicosis. However, the risk estimates are not stable, as shown by the very wide confidence intervals, and the differences are not statistically significant.

	OR (95% Confidence Interval)		
Silicosis	≤10 Pack-years	10-29 Pack-years	(30 Pack-years
No	1.0	5.1 (1.2, 22.4)	11.7 (2.7, 49.8)
Yes	4.1 (0.3, 52.3)	7.9 (1.4, 46.4)	48.9 (8.5, 281.4)

These data utilizing radiological diagnosis of silicosis support the silicosis/lung cancer hypothesis. The reasons for the diametrically opposed results between the autopsy results (Hnizdo and Sluis-Cremer, 1991) and the radiographic results (Hnizdo et al., 1997) are unclear.

b. Chinese Workers

In China since 1963, registries of employees with silicosis have been required by law in workplaces with silica exposure (Chen et al., 1992). What is not clear is the definition of silica exposure. Hua et al. (1994) indicate that since 1963, all workers exposed to dust containing >30% silica are required to obtain an annual medical evaluation and chest film. The criteria for screening and diagnosis are the same throughout China, and all use the Chinese Roentgenodiagnostic Criteria of Silicosis. Dosemeci et al. (1993) found that for the workplaces in the McLaughlin et al. (1992) study, silica content ranged from 1% to 37% during the years 1950 to 1988. Only one reading was over 30%, and only one over 20%. Wu et al. (1992) found the upper range of silica content in the iron-copper mine to be <30%. Silica content estimated from three samplers each from six mines had an upper range of 4.6% to 30% (median = 20%) and a lower range of 1.5% to 18.1% (median 3.2%). Given that silica content was consistently less than 30% in these workplaces, it is not clear that the entire working populations in the Chinese studies were screened for silicosis, or how the silicotics were ascertained. As a result, there is possible enumeration bias in these studies. In light of that possibility, the results of the Chinese studies of lung cancer risk among silicotics should be given less weight than other "Category One" silicotic studies discussed in this Review.

As a preliminary step in the joint Sino-American pneumoconiosis research efforts, Hodous et al. (1991) compared x-ray readings of 150 chest films; half of silica-exposed workers

from China and half of mostly coal miners from the U.S. There was general agreement between the Chinese radiological categories and ILO categories for pneumoconiosis. For small opacities, the Chinese readers tended to read slightly more disease, but there was agreement on the major categories in two-thirds of the films. The authors concluded that there was a valid correspondence between Chinese and American interpretation, so that the Chinese studies are suitable for epidemiological research.

The studies by McLaughlin et al. (1992) of Chinese workers provide little information on the basis for radiological diagnosis of silicosis, saying only that there is a silicosis registry at each factory and that workers with silicosis are examined and x-rays taken every 2-3 years to monitor their condition. Information on the criteria for diagnosis is not provided, although the authors do say that silicosis and silica exposure showed a strong association. Comparison of silicotics and nonsilicotics was adjusted for age and smoking. The results are inconsistent, showing a 3-fold risk among iron-copper mine silicotics, but no increased risk among pottery workers or tungsten miners. The ORs are reflected in the prevalence of silicosis among cases and controls: 20%/10% among iron-copper miners; 16%/12% among pottery workers; and 22%/23% among tungsten miners.

Dong et al. (1995) indicated that all workers underwent periodic health exams for silicosis between 1963-1985, so enumeration bias is unlikely. Otherwise, the methods are presumably the same as McLaughlin et al. (1992). Lung cancer risk among all silicotics showed a 2.1-fold excess overall, and a monotonic increased risk by Chinese radiological Categories One, Two and Three to 1.97 (21 observed), 2.34 (10 observed) and 2.55 (4 observed), respectively. Lung cancer risk was significant among silicotics only for those with 20 or more years since first employment, but not those with <20 years (SRR = 0.87). The authors suggest the lung cancer risk among silicotics may be underestimated because of high mortality from silicotuberculosis and early death from tuberculosis and cor pulmonale, which accounted for 70% of all deaths. Smoking information was available but was not used in this analysis where steelworkers were the referent population. However, smoking is unlikely to explain these risks because of the small effect of smoking in this population and because of the 2.5-fold increased risk ratios. On the other hand, the RR in the highest exposure category is not statistically significant, and all of the lower confidence intervals are close to one, so adjustments for smoking would likely result in marginally significant (or nonsignificant) RRs using the lower confidence interval instead of the point estimate.

The Chinese studies of silicotics are contradictory, with two showing no association of lung cancer risk and silicosis, and two reporting significant associations. The unanswered questions about these studies are whether there is selection bias in silicosis ascertainment for the registries, and the nature of the diagnosis for silicosis. As a result, these studies on balance neither support nor detract from the silicosis/lung cancer hypothesis.

c. U.K. Pottery Workers

In the initial findings from the study of U.K. pottery workers, Cherry et al. (1995) evaluated the risk of lung cancer among workers with at least 1 chest radiograph (about 13% of cases and controls had missing radiographs). Among the lung cancer cases with radiographs, 7% had category ≥1/0 compared to 5.3% of the referents. This study meets all the criteria for an adequate silicotic study except for loss of subjects without radiographs (which appears to be a random loss), and the reduced certainty associated with radiographic diagnosis of silicosis. After adjustment for years worked and smoking, the OR for silicotics was 1.54 (0.40, 5.85), and the authors conclude pulmonary fibrosis was not associated with lung cancer.

d. Sardinian Silicotics

Carta et al. (1991) assessed mortality of all Sardinian silicotics diagnosed between 1964-1970 with follow-up to 1988. The cohort of 724 subjects included all incident cases, and ≥1/0 diagnosis was based on blinded review of standard radiographs. Thus, bias due to disability diagnosis should not occur. There were 22 lung cancer cases. Using expected lung cancer rates based on the regional population, the SMR for lung cancer in this cohort was 1.29 (0.85, 1.96). In a nested case-control analysis, 88 controls selected from approximately 6,000 male workers admitted to the hospital over the same time period as the cases, were matched on year of birth, year of entry, and smoking status. Analysis by radiographic category and cumulative exposure to respirable silica (gh/m^3) showed no association with lung cancer. The authors found a strong association between lung cancer and severity of airflow obstruction (measured as $FEV_1/VC\%$) that was independent of smoking and severity of radiological silicosis. These data do not support the silicotic/lung cancer hypothesis, as lung cancer was not associated with either severity of radiological diagnosis of silicosis or with cumulative exposure to silica dust among silicotics.

This is the only cohort of silicotic workers where airflow obstruction is reported, although there are a number of population-based studies reporting a similar association between lung cancer and airway obstruction (Cohen et al., 1977; Skillrud et al., 1986; Tockman et al., 1987). Carta et al. (1991) did not analyze the association of silicosis, silica exposure, and dust exposure with airway obstruction. Therefore, it is not clear on what basis they assert that these are independent effects. However, several investigators (Wiles et al., 1992; Irwig and Rocks, 1978) have shown an independent effect of dust on airway obstruction, providing some support for the potentially confounding effects of dust exposure in assessing lung cancer mortality among silicotics.

B. Category Two: Studies that Have Significant Limitations and Do Not Meet the Criteria for Inclusion

Discussed below are studies on which IARC (1997) relied because of the absence of occupational confounders, but which we do not consider useful in testing the silica/lung cancer

or silicosis/lung cancer hypotheses because they do not meet one or more of the criteria for inclusion. In addition, we also discuss the analysis of lung cancer risk among silicotics in de Klerk and Musk (1998), which was published after the IARC Working Group meeting.

These studies have several characteristics in common:

- They are all cohort studies with an external referent group. Hence, they address the question of whether the study group is experiencing increased mortality compared to a population that may differ significantly in respects other than exposure to silica.

- The workers are generally free of exposure to occupational carcinogens, although some subgroups do have confounding exposures.

- These studies are generally free of selection bias, although there is incomplete enumeration in studies of silicotics (Amandus et al., 1992; Partanen et al., 1994), and Danish stone workers (Guenel et al., 1989b).

- Smoking information is generally lacking or limited, so there is probable confounding from smoking, as the prevalence of smoking is generally high among blue collar workers and is very high among the lung cancer cases (as in the studies of Costello and Graham, 1988 and Costello et al., 1995).

- Finally, none of the studies used quantitative estimates of exposure to evaluate possible E-R trends, although some used years worked as a surrogate.

1. Studies of Silica-Exposed Workers

a. Refractory Brick Workers

Merlo et al. (1991) studied 1022 Italian refractory brick workers employed between 1955 and 1977 with follow-up to 1986. The surrogate exposure variable was tenure. SMR was increased to 1.9 among the 21 lung cancer cases with greater than 20 years latency, but in this group there was no apparent difference in risk between those with <20 years tenure and those with ≥20 years tenure. The increased risk in those workers with 20 or more years since first exposure could be explained as readily by coincident latency with smoking as by exposure to silica. Lung cancer risk was significantly elevated (SMR = 1.77) among those first employed prior to 1957 (before there were environmental improvements in the factory and when silica exposures were highest), compared to those first hired after 1957 (SMR = 1.23). The authors suggest this provides "plausibility of a causal role played by crystalline silica in lung cancer development." Smoking prevalence was similar among active employees in 1984 compared to all Italian males. Indirect adjustment for smoking suggested to the authors that smoking

contributed only 1.8% to the excess lung cancer mortality. The authors state that the lack of a smoking effect is corroborated by low mortality from emphysema (3/40 deaths of NMRD) and cardiovascular diseases (SMR = 0.93). They conclude that the "lack of major occupational confounding factors and selection biases, along with the irrelevant effect of smoking habits" supports a causal link between lung cancer and exposure to silica. IARC (1997) agreed, but noted there is no information on silica concentrations or on conversion of quartz to cristobalite.

This study has several significant limitations that severely limit its usefulness in testing the silica/lung cancer hypothesis. For one thing, there is no E-R analysis, and tenure is an inadequate surrogate because of the apparent difference in exposures before and after 1957. Comparison of lung cancer mortality by date of hire before and after 1957 is by itself not a suitable E-R analysis for several reasons. To compare SMRs, the age distribution should be similar. However, the pre-1957 group clearly is older based on higher mortality: There is almost twice the number of deaths in the pre-1957 group although the person years of observation is 37% higher in the post-1957 group. Furthermore, if a comparison is to be made, it should be between groups with the same latency, tenure, and length of follow-up. The maximum latency and follow-up for the post-1957 group is 29 years, and the minimum is 9 years. By contrast, for the pre-1957 group, the minimum latency and follow-up is 29 years; the maximum is 55 years. So it is not possible to tell whether the slightly lower SMR in the post-1957 group is due to a too short latency and/or follow-up. In addition, seven of the 28 lung cancer cases had latencies <20 years, and therefore should be excluded in assessing silica as an etiological agent. These cases are not identified as to date of hire.

The authors' assessment of the role of smoking also is inadequate. Smoking prevalence is based on 1984 data of 28% (295/1,050) of the cohort. The smoking prevalences among those employed in 1984 cannot represent with any degree of reliability or precision the smoking characteristics of those workers hired between 1931 and 1957, a generation or more before the smoking prevalences were ascertained. The authors also tried to account for smoking effects indirectly by observing that there were only 3/40 deaths from emphysema in the cohort, and the SMR from cardiovascular disease (CVD) was only 0.93. This indirect method of accounting for smoking is based on the idea that if the increased risk of lung cancer among the exposed cohort is due to excess smoking, then other smoking-related causes of death also should be elevated -- especially lung cancer, emphysema, and laryngeal cancer, but also coronary heart disease, bronchitis, and cancers of the pancreas, esophagus, bladder, and kidney (Steenland et al., 1984).

Like the indirect Axelson-type adjustment, the use of other smoking-related causes of death is a crude measure of possible smoking effects. For a number of reasons, such an adjustment for smoking must be viewed with some skepticism. For one thing, the effects of smoking in the exposed cohort may vary from one study to another because of differences in the definition of smoker, differences in age, and differences in length of follow-up (Steenland et al., 1984). Moreover, as shown in the table on page 7 above, mortality ratios for the same smoking-related cause of death have a wide range from one study of smokers to another. In addition,

some smoking-related causes of death often are not reported (frequently because of small numbers) or are collapsed into a larger category where not all causes have the same association with smoking.

Even apart from the foregoing limitations on this type of adjustment for smoking, the data on smoking-related causes of death from Merlo et al. (1991) do not unequivocally demonstrate the absence of an effect from smoking. SMRs for the total cohort and the pre-1957 group of refractory brick workers studied by Merlo et al. (1991) are shown in the following table:

SMRs for Smoking-Related Diseases in Merlo, et al. (1991)

	Refractory Brick Workers	
Cause of Death	**SMRs (Obs.)**	
	Pre-1957 Hires	**All**
Lung Cancer	1.77* (17)	1.51 (28)
Laryngeal Cancer	Not reported	1.93 (5)
Esophageal Cancer	Not reported	1.18 (esophagus & stomach) (12)
Bladder Cancer	2.65 (4)	2.78* (7)
Pancreatic Cancer	Not reported	1.44 (3)
Cardiovascular Disease	1.14 (62)	0.93 (80)

* indicates that lower 95% confidence interval is >1.

Only a few causes of smoking-related death could be evaluated by Merlo et al. (1991). Those causes should not all be elevated if we accept the authors' contention that <2% of the excess lung cancer mortality in their cohort can be attributed to smoking -- because, if their contention were correct, smoking could contribute only negligibly to other smoking-related causes of death. Except for cardiovascular disease, however, mortality is increased, albeit only slightly, for all these causes of death. For the pre-1957 hires, the two causes of death other than lung cancer for which data are presented are elevated. Because of small numbers, only bladder cancer in the total cohort and lung cancer in the pre-1957 hires are statistically elevated. Contrary to the authors' conclusion, this analysis is suggestive of a possible smoking effect. However, the data are too sparse to clearly delineate the role of smoking. Another problem with

this type of adjustment is deciding whether the excesses are large enough to count, and whether they are due to smoking.

In sum, neither of these attempts to control for smoking indirectly is considered reliable, and the potential role of smoking remains unclear in the study by Merlo et al. (1991), as does the possible role of silica exposure. For that reason, and because a meaningful E-R analysis is not possible, this study does not meet the criteria for inclusion, and is not useful for testing the silica/lung cancer hypothesis.

Dong et al. (1995) studied Chinese refractory brick workers. Smoking histories were available, but the reliability of smoking histories is in question, since smokers in the cohort had a similar risk of lung cancer as nonsmokers. Standardized Rate Ratios (SRRs) were 1.58 and 1.37 for smokers and nonsmokers, respectively, and 2.34 and 2.13 for smoking and nonsmoking silicotics. Lung cancer risk was increased in the workers with 20 or more years since hire, but not in the workers with less than 20 years since first exposure. This association would be expected by smoking, since workers with the longer latency from first exposure would likely have a longer latency for smoking as well. This study has no E-R analysis, not even an analysis by latency and tenure. Since smokers showed a similar risk of lung cancer as non-smokers, (about a 2-fold increased risk in both cases), and since there was no adjustment for smoking in the analysis and no estimate of exposure (even by years worked) this study is not appropriate for testing the silica/lung cancer hypothesis.

b. Stone Workers

Costello and Graham (1988) reported on Vermont granite workers where there was 50% increased lung cancer mortality in the shed workers with $\geq$15 years latency and $\geq$30 years tenure. All 84 of the 118 lung cancer cases with known smoking histories were smokers, and the authors concluded that smoking is an essential ingredient in the occurrence of lung cancer in this cohort. The higher SMRs in the pre-1940 period when exposures were high compared to the lower SMRs in the post-1940 years when exposures were lower is suggestive evidence of a silica lung cancer association. However, this comparison does not account for possible differences in smoking and is not appropriate unless latency, duration of exposure, and time of follow-up are similar. When latency and tenure are comparable, the lung cancer SMRs for those hired before and after 1940 were similar, as shown below:

Lung Cancer SMRs in Granite Shed Workers with 25-39 Years Latency by Years of Employment (Costello and Graham, 1988)		
	Tenure	
Period of Employment	10 - 29 Years	≥30 Years
Pre-1940	1.27 (0.51, 2.62)	0.78 (0.31, 1.60)
Post-1940	1.91 (1.04, 3.21)	1.22 (0.25, 3.56)

Indeed, there is a suggestion of a reverse trend in SMRs -- with lower SMRs in the high silica-exposure years compared to the post-1940 period when exposures were lower. Although these differences are not statistically significant, these data clearly do not provide support for an E-R trend and do not support IARC's conclusion that the data from Costello and Graham (1988) are indicators of an E-R trend.

Because of the absence of E-R analyses and the lack of control of smoking, this study does not meet the criteria for testing the silica/lung cancer hypothesis.

Costello et al. (1995) reported on a cohort of crushed stone workers where analysis was by latency and tenure in the total cohort and by rock type (limestone, granite, traprock). The only significant result was a 3.5-fold excess risk of lung cancer from 7 deaths in the group of granite workers having ≥20 years latency and ≥10 year tenure. There were no lung cancer cases among granite workers with <10 years tenure, so the association with tenure could not be determined.

Two internal NIOSH reports on this cohort provide additional analyses. Smoking status was known for 30/51 lung cancer cases, and 28 of the 30 were smokers. In one internal NIOSH report, nested case-control analyses matched on smoking showed no E-R trends with years worked (Costello et al., 1987). In the other report, there was an internal analysis evaluating workers in high exposed jobs while adjusting for age, date of hire, latency and rock type. No association with lung cancer was observed, although power was reduced. The authors (Costello et al., 1990) concluded that because of exposure misclassification, the silica/lung cancer hypothesis could not be tested. Exposure time was over a 50 year period, and the difference in exposures between rock types makes tenure an inappropriate surrogate for exposure. The only statistically significant finding was increased risk in lung cancer among the small subsample of granite workers. Whether this excess is attributable to smoking, to inadequate referents, to a chance finding among many comparisons, or to silica exposure remains to be determined.

Guenel et al. (1989a,b) reported on lung cancer incidence among Danish stone workers having no known exposure to other occupational carcinogens. Individual-level smoking was not known, so regional referent population rates were used for expected rates, which was said to adequately adjust for smoking. The authors concluded that Standardized Incidence Ratios (SIRs) were related to group-level silica dust concentrations measured in some of the stone worker occupations. However, for several reasons, this conclusion is not convincing. First, there were no data on exposure duration for any of the study population. Second, the silica concentrations that were measured were not necessarily at the work sites of the study population; they showed an 8 - 40-fold range of concentrations; and they could not be correlated with worker exposure. Third, there was no information on work histories, date of hire, or duration of employment. The cohort was enumerated from union lists, census lists and other sources, but consideration of the numbers of workers enumerated on several census lists indicates that >40% of all workers were not included in the cohort. Clearly, this study has potentially severe biases, so the risk estimates are unreliable.

2. Silicotic Studies

IARC (1997) considered two studies of silicotics to be important in evaluating the potential association of silica and lung cancer: One was a study of silicotics in the dusty trades industries in North Carolina (Amandus et al., 1991, 1992, 1995); the second was a study of silicotics in Finland (Partanen et al., 1994). These two studies are more a possible test of the silicosis/lung cancer hypothesis than the silica/lung cancer hypothesis.

a. North Carolina Dusty Trades

Amandus et al. (1991) reported on the mortality of 760 silicotics diagnosed between 1940 and 1983 as part of the North Carolina pneumoconiosis surveillance program for dusty trades workers. There were 33 lung cancer deaths among white males with a 2.6-fold increased SMR compared to U.S. white males. When silicotics with occupational exposure to carcinogens were excluded, there was nearly a 3.2-fold excess risk of lung cancer among the 10 silicotics who had ever smoked compared to nonsilicotic metal miners, and a nonsignificant RR of 1.8 among eversmokers compared to nonsilicotic coal miners. The authors concluded that these results are consistent with the hypothesis of an association between silicosis and lung cancer.

The highest risk of lung cancer was in those diagnosed with lung cancer <5 years after silicosis diagnosis (a total of 8 cases; SMR = 3.4), so detection bias was thought to explain some, but not all, of the excess risk of lung cancer.

Because of the potential bias from misclassification of silicosis based on small radiographs in the 1991 study, Amandus et al. (1992) re-evaluated standard radiographs for cohort members where available. In the reanalysis of the original 760 dusty trades workers classified as silicotic, only 370 radiographs (49%) were available for reading by three "B"

readers. When these 370 radiographs were re-read, there were 104 nonsilicotics, 160 simple silicotics, 83 with progressive massive fibrosis (PMF), and 23 unreadable x-rays. Thus, of the original 760 silicotics, only 46% (370-23/760) were available for analysis, a loss of 54% of the original cohort. The misclassification error rate in the original study was found to be 28% false positives (104/370) and 3% false negatives (3/107 nonsilicotic radiographs were re-read as silicotics).

In the cohort with reclassified radiographs, there was no apparent increased risk of lung cancer among the 2 nonsilicotics who died of lung cancer (SMR = 1.0). The 7 silicotics who died of lung cancer and had no other occupational exposures to known carcinogens did not have a statistically significant excess risk (RR = 1.5) compared to nonsilicotics. The SMR for simple silicotics was 2.4 (not statistically significant). On the basis of these findings, Amandus et al. (1992, 1995) concluded that lung cancer rates were increased in North Carolina silicotics and that the increase was not due to age, exposure to other occupational carcinogens, detection bias, or smoking.

The North Carolina dusty trades study merits careful examination because of the claim that most of the biases peculiar to studies of silicotics have been avoided (IARC, 1997; Amandus et al., 1995). The critical points are as follows:

i) The silicotics are workers in the North Carolina dusty trades with known occupational silica exposure in a specific job and workplace. This is clearly an advantage over most registry studies where exposure assumptions are based only on industry and the specific job and workplace are not known. Moreover, silica exposures of the dusty trades workers were generally high, approximately 1 to 2.5 times the current PEL for quartz (Rice et al., 1986). However, Amandus et al. (1992) provide no E-R analysis for lung cancer using these data.

ii) Misclassification of silicosis was minimized, because silicosis was defined radiographically and not, for example, on the basis of smoking-related health problems, as is the case with compensation applicants. However, the initial diagnoses when re-evaluated showed a 28% error rate of false-positives, and a 3% error rate of false-negatives.

iii) Reclassification of the radiographs reduced the number of subjects in the study by more than half and resulted in a reduction in the number of lung cancer cases from 33 (SMR = 2.6) to 10. Of these 10 lung cancer cases, 2 were nonsilicotic cases (SMR = 1.0), and 8 were silicotic cases (SMR = 2.1). The loss of about two-thirds of the lung cancer cases and over 50% of the subjects because of unavailable radiographs severely restricts the ability to adjust for smoking in this study, may introduce biases due to significant loss of subjects from the original cohort, and reduces the number of subjects to a very small number.

iv) If silicotics are at increased risk of lung cancer, it is not clear why this risk went down instead of up when false positive silicotics were removed. (Moreover, in the reclassified cohort, there were no lung cancer deaths -- although only 0.6 were expected -- among the 67 subjects classified as having PMF, the most severe stage of pneumoconiosis.)

v) Individual data were available on smoking and employment history, so adjustments could be made for confounding exposures to cigarette smoke and occupational carcinogens. Workers with known exposure to occupational carcinogens were excluded from some of the analyses. This reduced the number of reclassified silicotic lung cancer cases from 8 to 7.

vi) Intensity and duration of smoking were not known, so only the category "eversmoker" was used. Because of the small numbers of cases, the authors were "prevented [from] adjusting rate ratios for cigarette smoking habit" (Amandus et al., 1992). Of the 7 remaining silicotics with lung cancer and without other occupational exposures, 5 are known to be smokers. There were no lung cancer cases among the silicotics who are known never to have smoked.

vii) If there were detection bias in the reclassified cohort, lung cancer mortality would be expected to be high within a short time after onset of symptoms (or diagnosis of silicosis). Among the lung cancer cases where silicosis was determined after leaving employment, lung cancer mortality was significantly increased when death occurred less than 10 years after diagnosis of silicosis, but was not increased when death occurred more than 10 years after diagnosis of silicosis. This suggests the possibility of detection bias -- i.e., some proportion of the silicotics may have requested post-employment compensation examinations because of the presence of symptoms related to lung cancer or smoking. However, this manner of testing for bias is only a crude surrogate; lung cancer mortality may take a long period of time for death to occur even if it is related to smoking. The best test of detection bias is to evaluate the participation rate of all dusty trades workers. If the participation rate is close to 100%, then detection bias would not be a factor. About 15% of the original 655 while male silicotics (and 15% of lung cancer cases) were diagnosed after leaving employment, suggesting participation during employment could have been about 85% or less. On balance, we are left with uncertainty about possible detection bias. The most that can be said is that detection bias and nonparticipation bias may explain some of the excess risk among silicotics in the reclassified cohort.

viii) Data were available on a reference group of nonsilicotics with comparable risk factor characteristics, namely metal miners and coal miners. However, these referent groups were used only for the original cohort of silicotics, not in the

cohort of reclassified silicotics. Moreover, in the original cohort comparisons to the metal miner and coal miner referent groups, the risks were quite variable depending on which referent group was used: The RR ranged from 1.8 in the comparison to nonsilicotic coal miners to 3.2 (significant) in the comparison to metal miners, even though the metal miners themselves had an increased lung cancer risk of 1.44. Coal miners do not have increased risk of lung cancer, so the direction of the disparity in these risk estimates is puzzling.

Amandus et al. (1995) suggest that their study is relatively free of the major shortcomings that characterized previous studies of silicotics and is consistent with the hypothesis of an association between silicosis and lung cancer. However, to avoid problems of misclassification of silicosis and confounding from occupational carcinogens, the authors reclassified and reduced the cohort so that the number of lung cancer cases became too small to adjust for smoking effects even if smoking histories were available in sufficient detail. With the severe reduction in the study population following reclassification, the results are no longer significant, and the major shortcomings of silicotic studies can no longer be addressed. Some amount of detection bias appears to be present and is not adjusted for in the analysis. The effects of volunteer participation bias and loss to follow-up bias are unknown. Consequently, the results of this study cannot be interpreted and cannot be used to support or detract from the silicosis/lung cancer hypothesis.

b. Finnish Silicotics

Partanen et al. (1994) reported on the incidence of cancer among 1127 Finnish silicotics diagnosed between 1936 and 1977. Only 811 (72%) of this group were followed-up between 1953-1991. The major causes of exclusion were death or emigration (20%) and missing information (8%).

The SIR for lung cancer was significantly increased to 2.89 (2.35, 3.48) with 101 cases, representing 53% of all cancers. The lung cancer risk was consistently elevated across various industries. Smoking histories were known on 41 of the 101 lung cancer cases; all but one had smoked. The SIR for the 25 smokers was 6.7, for the 15 ex-smokers was 1.9, and for the 1 nonsmoker was 0.44 when compared to Finnish population incidence rates. The authors concluded that this study supports an association between silicosis and lung cancer.

Kurppa et al. (1986) studied mortality in this same cohort and concluded that it was not possible to infer whether exposure to quartz or silicosis was causally related to cancer risk, or to determine whether smoking could partially explain the results. A similar conclusion is applicable to the study by Partanen et al. (1994), as the roles of smoking and other potential occupational confounders (e.g., radon) could not be properly analyzed. In particular, it was not possible to determine whether quartz exposure potentiated the carcinogenic effect of smoking or occupational carcinogens, or whether nonsmoking silicotics had an elevated risk of lung cancer.

There was only one known nonsmoker among the lung cancer cases with an expected incidence of 2.3 -- too small a number to answer the question regarding nonsmokers. Moreover, the histology-specific SIRs resembled those of smokers, so smoking remains a viable alternative hypothesis.

The authors observe that "[o]n balance, there was little evidence of confounding of the lung cancer risk by tobacco smoking." If confounding occurred, they say, one would expect an increased risk of other smoking-related cancers. The authors suggest this did not occur, as "[t]he 1.9-fold (95% CI, 0.9 to 3.5) bladder cancer increase did not reach significance, and there was no excess whatsoever (SIR, 1.0, 95% CI, 0.7 to 1.7) for the pooled smoking-related cancers after exclusion of lung cancers."

As discussed in Section II.B.1. above, examining the rates for other smoking-related cancers cannot account adequately for the potential effects of smoking, because smoking-related risks for these diseases are much lower than the smoking-related risk for lung cancer. Furthermore, if data for smoking-related noncancers are considered along with the cancer incidence data, the question of confounding from smoking in this study remains a possibility, if not a probability. Relevant data for the cohort studied by Kurppa et al. (1986) and Partanen et al. (1994) are presented in the following chart:

	SIR (Partanen et al., 1994)	**SMR (Kurppa et al., 1986)**
Larynx	3/2.6 = 1.16 (0.24, 3.37)	--
Mouth, pharynx	3/4.1 = 0.72 (0.15, 2.14)	--
Esophagus	3/2.1 = 1.43 (0.29, 4.17)	--
Pancreas	1/4.3 = 0.23 (0.006, 1.30)	--
Kidney	4/3.1 = 1.29 (0.35, 3.30)	--
Bladder	10/5.3 = 1.89 (0.91, 3.47)	--
Sum	24/21.5 = 1.12 (0.72, 1.66)	
Cardiovascular disease	--	203/183.1 = 1.11 (0.96, 1.27)
Chronic bronchitis, emphysema, and asthma	--	27/5.6 = 4.78 (3.18, 7.04)

The very high SMR in the bronchitis and emphysema disease category is strong counter-evidence against the relatively variable and unstable findings for smoking-related cancers and suggests likely confounding by smoking in this cohort. The authors themselves estimate that such confounding could produce an upward bias of 50% in the lung cancer risk.

Similarly, there could have been confounding by exposure to occupational carcinogens. The role of occupational carcinogens is not known on an individual level in this study. Thus, as Partanen et al. (1994) acknowledge: "The extent of confounding from occupational exposures such as asbestos, radon, polycyclic aromatic hydrocarbons, and diesel exhaust remains unknown in the present data." This could be important because Kurppa et al. (1986) mention the presence of radon in underground mines and point to workers in the stone industry as probably the only subgroup without substantial exposure to other known occupational carcinogens.

There are a number of biases in the study by Partanen et al. (1994) that can affect the risk ratios to a largely unknown extent, and in some cases in an unknown direction. These include:

- *Misclassification of silicosis*: Partanen et al. (1994) indicate about a 10% false positive misclassification rate of silicotics based on clinical findings, which is a compensation-based diagnosis that could be related to smoking. In addition, there was an unknown proportion of mixed dust pneumoconiosis that could be due to asbestos. This misclassification was estimated to cause an upward bias of about 30% in the lung cancer SIR. Partanen et al. (1994) also indicate it is possible that only the most advanced cases of silicosis are included in the cohort, with less severe cases not included or not diagnosed. According to the authors, this potential bias would tend to accentuate the contrast between silicotics and the referent population but "would not materially have biased the cancer SIRs, because silicosis is rare in the national population, which served as the referent entity." This bias would, however, likely produce a higher concentration of lung cancer cases among those identified as "silicotic" than would be the case if individuals with less advanced cases of silicosis had been included in the cohort.

- *Detection bias*: Detection bias is particularly likely to occur in a register-based cohort such as the one studied by Partanen et al. (1994). For example, if ill health from incipient lung cancer triggered an examination to get compensation for silicosis, then the apparent lung cancer risk among silicotics would be elevated. This was not considered by the authors to be a large bias as lung cancer incidence did not increase until over 10 years after silicosis diagnosis. A more important bias, however, is the possibility that smoking-related illness triggered an examination and diagnosis of silicosis. In this instance, the bias is away from the null, the association will be confounded by smoking, and the proportion of smokers is likely to be elevated. Such detection bias is a likely occurrence in this kind of study.

- *Socioeconomic status bias (SES)*: Silicosis can be incapacitating, so one's ability to work (and one's salary) are likely to decline. Partanen et al. (1994) call attention to the possible

health effects of unemployment and reduced SES on disease, including lung cancer. The likely effect is to bias the risk upward.

Overall, the authors estimate that possible confounding by smoking (50%) and asbestos-related pneumoconiosis (30%) could have increased the risk of lung cancer by about 80%. The impact on lung cancer risk of other identified confounders and biases -- such as SES, occupational carcinogens, loss to follow up, incomplete enumeration (self-selection of the more severe cases of silicosis), and misclassification (false positives) -- could not be estimated.

c. Australian Gold Miners

de Klerk and Musk (1998) conducted a nested case-control study among Australian gold miners and determined the risk of lung cancer by comparing compensated silicotics with nonsilicotics after adjustment for smoking and bronchitis. The risk of lung cancer was increased among the silicotics (OR = 1.59, 1.10, 2.28) compared to controls after adjustment for smoking and bronchitis. This led the authors to conclude that if exposure is sufficient to cause silicosis, it is sufficient to increase the risk of lung cancer.

A major weakness in this study is that the diagnosis of silicosis was based on compensation claims which, in turn, reflected a combination of radiographic signs and other symptoms. While the criteria for awarding compensation had changed over the 33 years of the study, compensation was associated with both smoking and silica exposure. The authors concluded that "symptoms due to smoking may be increasing the likelihood of a worker making a successful claim for compensation for silicosis," either because of smoking-related disability or because of more severe smoking-related symptoms and radiographic changes. While the adjustments made for smoking and bronchitis strengthen the authors interpretation of a silicosis/lung cancer association, they may not provide complete adjustment for potential confounding effects of other symptoms and changes in diagnostic radiographic criteria over time. Since the magnitude of the bias in silicosis misclassification cannot be estimated, this study, like most registry-based studies, cannot properly be used to test the silicosis/lung cancer hypothesis.

3. Summary of Category Two Studies

IARC (1997) considered the studies of silica-exposed workers reviewed in Section B.1. above to be relatively free of confounding from occupational carcinogens. In general, this appears to be true, but confounding from smoking is not taken into account, there are no estimates of exposure (years worked is an inadequate surrogate of exposure), and there are no internal analyses except in one of the unpublished NIOSH reports on crushed stone workers where no association of silica exposure and lung cancer was observed. Thus, these studies are considered inadequate to test the silica/lung cancer hypothesis.

The three silicotic studies reviewed in Section B.2. should not be used to evaluate the silicosis/lung cancer hypothesis because of a number of biases and potential confounders that make interpretation problematic. The direction of the bias in the studies of North Carolina dusty trades workers is unknown, and smoking could have been a significant confounding factor. Bias and potential confounding appear to have caused an overestimation of risk in the study of Finnish silicotics. The compensation-based diagnosis of silicosis in the study of Australian gold miners introduces a potentially significant bias because the diagnosis is to some unknown extent affected by smoking disability. Accordingly, these three studies are considered inadequate to address the silicosis/lung cancer hypothesis.

IV. LUNG CANCER AND SILICA: THE QUESTION OF CAUSALITY

Epidemiology is an observational science. As such, it is not possible to control such things as the conditions of exposure, the presence or absence of confounding variables, or the composition of the study population (such as random selection). One can only observe and record what happens in real-life situations. Although determining whether an association is statistical or causal is a matter of judgment, there are accepted guidelines by which to judge the nature of an association.

There are two levels in assessing causality. The first is the level of individual studies. Are they suitable for testing the hypothesis? To be suitable the finding should not be due to chance or normal variation, should not be due to bias or a consistent nonrandom error, and should not be due to confounding, a kind of bias where a risk factor for lung cancer is also associated with exposure.

If results from individual studies are not due to chance and are relatively free of bias and confounding, then this body of evidence is assessed to determine whether the criteria of temporality, strength of association, biological gradient, consistency, and biological plausibility are met (Hill, 1965; HEW, 1964). If there is a meaningful statistical association, then the question becomes whether there is a causal association. Causality goes beyond statistical probability. None of the causal criteria alone can prove causality, although failing the temporality criterion can eliminate the possibility of a causal association.

The individual studies that meet the criteria for inclusion in a weight-of-evidence review have been discussed in Section III above.

- The studies dealing with the silica/lung cancer hypothesis are summarized in Table 1, and their results (as they relate to the consistency of the findings for strength of association and biological gradient) are summarized in Table 3. The results are presented visually in Figure 1.

- The studies dealing with the silicosis/lung cancer hypothesis are summarized in Table 2, and their results (as they relate to the consistency of the findings for

strength of association and biological gradient) are summarized in Table 4. The results are presented visually in Figures 2 and 3.

A. Temporality

A fundamental criterion for causality is that the exposure must occur prior to the adverse effect. For lung cancer, the exposure must occur 20 or more years before the diagnosis because of the long latency period. Many of the studies have not considered latency explicitly, making it difficult to determine whether adequate time from first exposure has elapsed for the development of lung cancer. Nonetheless, it does not appear that consideration of temporality will be a significant factor one way or the other in evaluating the potential association between silica exposure (or silicosis) and an increased risk of lung cancer.

B. Strength of Association

The stronger the association (*i.e.*, the greater the magnitude of the difference in risk between high and low exposure groups), the less likely the difference is due to chance, confounding, or bias. Weak associations detract from a determination of a causal association. A weak association is commonly considered to be a RR of less than 1.5 - 2.0 (Wynder, 1990).

1. The Silica/Lung Cancer Hypothesis

The associations between silica exposure and silicosis, pneumoconiosis, and silicotuberculosis are generally strong. By contrast, the association between silica exposure and lung cancer is either weak or nonexistent. Of the studies listed in Table 3, eight showed no association between quartz exposure in the high exposed category and lung cancer, and three showed only a weak association that was not statistically significant. Only one of the studies showed a statistically significant association between lung cancer and exposure to quartz in the highest exposed group (Hnizdo and Sluiz-Cremer, 1991), and that association no longer was significant when an adjustment for silicosis was made in a follow-up study using a matched set of controls (Hnizdo et al., 1997). Checkoway et al. (1997), showed a suggestive increased risk of lung cancer among diatomaceous earth workers with high exposure to cristobalite, but the true association is unclear because of potential confounding and misclassification bias. Finally, while Cherry et. al. (1997) found a relatively weak association between increased lung cancer risk and employment in pottery jobs where there may have been exposure to cristobalite, the use of 90% confidence intervals in that study indicates only marginally significant results.

The weakness of the association between silica exposure and lung cancer is particularly striking given the much stronger associations between silica exposure and NMRD seen in many of the same cohorts -- as illustrated in the following chart that has been prepared from several of the most important studies where risks of both lung cancer and NMRD can be compared.

Author (RR, exposure group)	Risk Ratios (95% confidence intervals)	
	Lung Cancer	NMRD
Reid and Sluis-Cremer (1996)		
SMR: all	1.40(1.18, 1.65)	3.06(1.92, 4.64) TB 21.2(12.2, 34.6) Silicosis, pneumoconiosis, asbestosis
Chen et al.(1992); cohort for McLaughlin et al (1992)		
RR: high exposure group (1972-1989)	1.10(0.90, 1.4)	13.6(8.9, 21) Pneumoconiosis
Chen et al (1992)		
SMR: Tungsten miners	0.45	50.1 Pneumoconiosis
SMR: Iron-copper miners	0.79	15.9 Pneumoconiosis
SMR: Pottery workers	0.78	29.7 Pneumoconiosis
McDonald et al. (1997)		
Prevalence: >4000 mg/m^3-years	1.7%	13.6% (>1/0 silicosis)
Cherry et al. (1995), cohort of Cherry et al (1997)		
SMR: all	1.28(1.04, 1.57)	2.04(1.62, 2.55) NMRD
Checkoway et al. (1997)		
SMR: high exposure, lagged 15 years	2.15 (1.08, 4.28)	5.35(2.23, 12.8) NMRD
Steenland and Brown (1995)		
SMR:>48,000 dust days	1.31(0.87, 1.90)	8.87(6.45, 11.9) Pneumoconiosis, other Respiratory disease

Considering the body of studies as a whole, the strength of association between silica exposure and lung cancer is weak, a fact that detracts significantly from the silica/lung cancer hypothesis.

2. The Silicosis/Lung Cancer Hypothesis

As shown in Tables 2 and 4, eleven studies (or nine cohorts) meet the criteria for inclusion in an analysis of the association between silicosis and risk of lung cancer. In each case, silicotics -- diagnosed either by autopsy or by radiograph -- were compared to nonsilicotics for the risk of lung cancer,

Eight studies used radiological definitions. The studies of Chinese iron-copper miners (McLaughlin et al., 1992) and refractory brick workers (Dong et al., 1995) showed moderately strong 3-fold and 2.5-fold excess risks of lung cancer among silicotics compared to nonsilicotics, though only McLaughlin et al. (1992) was statistically significant. The UK pottery silicotics

(Cherry et al., 1995) showed an OR of 1.5 that was not significant using 90% confidence intervals (0.40, 5.95). South African gold miner silicotics studied by Hnizdo et al. (1997) also showed an OR of 2.45 or 2.1 when compared to nonsilicotics after adjustment for smoking in the first case and for both smoking and silica exposure in the second case. The OR reflecting both adjustments was not statistically significant. The other radiological studies of cohorts (Chinese tungsten miners and pottery workers studied by McLaughlin et al, 1992; South African gold miners studied radiographically by Hessel et al., 1986; and Sardinian dusty trades silicotics studied by Carta, et al., 1991) showed no associations between silicosis and lung cancer.

Three South African studies (Hessel et al., 1986; Hessel et al., 1990; and Hnizdo and Sluis-Cremer, 1991) evaluated risk of lung cancer using autopsy diagnosis of parenchymal and pleural silicosis. There were no significant excess risks associated with either category. The highest point estimate of risk for parenchymal silicosis was a nonsignificant OR of 1.49 (Hessel et al., 1986); the other ORs were at the null value. The highest OR for pleural silicosis was 1.2 (Hnizdo and Sluis-Cremer, 1991) while the ORs were <1 for the other two studies. In a follow-up study, Hnizdo et al. (1997) presented data reflecting radiological diagnoses of silicosis. As noted above, they found a 2.45-fold increased risk in a case-control analysis of radiological silicosis after controlling for smoking and a nonsignificant 2.1-fold increased risk after controlling for smoking and silica exposure (Hnizdo et al., 1997). These results are internally inconsistent -- presumably reflecting the fact, as noted by the authors, that the radiological results are "problematic" and "inconclusive." The best interpretation of these results is that an association between silicosis and lung cancer has not been shown in this subset of South African gold miners.

Overall, in the eleven studies or cohorts where silicotics and nonsilicotics are compared, two show a moderately strong association between silicosis and lung cancer, with only one of these associations being statistically significant. In the other nine studies, the RRs are either around the null value or slightly elevated but not in a statistically significant way.

Table 4 and Figure 3 display the results of silicotic studies by dust exposure and by severity of silicosis. There are four studies evaluating the association of lung cancer risk with increasing severity of silicosis. Parenchymal silicosis is defined by autopsy in two studies and by radiological diagnosis in the other two. Two of the studies show RRs that are less than one in the most severe category of silicosis (Hessel et al. 1990; Carta et al, 1991). The other two show risks of lung cancer that are increased -- 1.6-fold for subjects with marked parenchymal silicosis in Hessel et al. (1986) and 2.6-fold for Chinese radiological category 3 silicotics in Dong et al. (1995). But the trend is not statistically significant in Hessel et al. (1986), and the significance of the trend is difficult to assess in Dong et al. (1995). Thus, the point estimates suggest no association with lung cancer in the category of highest silicosis severity in two studies, a weak nonsignificant association in the third study, and a moderate association in the fourth study. At the same time, none of the studies where exposure information for the silicotics was available

showed a significant trend for the risk of lung cancer to increase as exposure increased. Indeed, in most cases, there was a nonsignificant inverse trend.

In sum, in the studies where data on severity of silicosis or dust exposure are presented, the lung cancer risks for the silicotic workers who should be at highest risk of lung cancer based on exposure or severity of silicosis consistently are essentially indistinguishable statistically from the risks for nonsilicotics: The point estimates of risk are as often below 1 as above 1. These consistently weak associations detract from the silicosis/lung cancer hypothesis.

C. Biological Gradient: Exposure-Response (E-R) or Dose-Response (D-R)

The presence of a trend for the risk of lung cancer to increase as silica exposure increases would provide persuasive evidence of a causal association for the silica/lung cancer hypothesis. As IARC (1997) observes, an E-R trend is a "strong indication of causality." Similarly, trends for lung cancer risk to increase with increasing severity of silicosis or with increasing exposure among silicotics would support the silicosis/lung cancer hypothesis. Conversely, the absence of an E-R trend usually detracts from the hypothesis of a causal association, particularly if the lack of such a trend is a consistent finding in many studies.

1. The Silica/Lung Cancer Hypothesis

Figure 1 visually displays E-R trends in studies of silica-exposed workers that have a minimum of bias or confounding. The great majority of the studies show no convincing E-R trend. Moreover, as discussed below, the possible exceptions show, at best, weak associations in the highest exposure category, and these, for the most part, are not statistically significant.

- The study of Chinese pottery workers by McLaughlin et al. (1992) shows a nonsignificant trend for lung cancer risk to increase with increasing silica exposure. However, there is potential confounding from PAHs as well as possible exposure to cristobalite -- as suggested in the study of U.K. pottery workers by Cherry et al. (1997).

- The study of U.K. pottery workers by Cherry et al. (1997) found a statistically significant increased risk of lung cancer in workers with the highest intensity of exposure, notably among those workers thought to have been exposed to cristobalite in firing or post-firing jobs. However, the authors provided no data to evaluate the possible existence of an E-R trend among this group of workers as the analysis was "ever worked" versus "never worked," and statistical significance was assessed using 90% confidence intervals, so the possibility of a chance occurrence remains. Using quartz as the exposure metric, there were no E-R trends associating increasing lung cancer risk with increasing cumulative exposure or with increasing maximum exposure after excluding effects of possible

exposure to cristobalite. The authors conclude that "the only risk factor so far identified in this study was work in firing or post firing occupations."

- The study by Checkoway et al (1997) of diatomaceous earth workers exposed to cristobalite shows no E-R trend in lower exposure categories and about a 2-fold RR in the highest exposure group. Whether the risk is marginally significant or not significant depends on whether workers potentially exposed to asbestos are included. (It is not significant when they are excluded.) The excess risk in the high exposure group also may be explained by confounding from smoking or may be due to unaccounted for asbestos exposures and misclassification of early silica exposures in the workers hired prior to 1930. As a result there is no clear-cut unconfounded E-R trend, and the risk of lung cancer cannot be unambiguously attributed to cristobalite exposure.

- Reid and Sluis-Cremer (1996), Hnizdo and Sluis-Cremer (1991), Hnizdo et al. (1997), and de Klerk and Musk (1998) show somewhat similar E-R trends for South African and Australian gold miners (if log exposure is used as the exposure metric for the Australian cohort and only point estimates of effect are considered). In the Australian study, there is a question about whether the one significant trend with log exposure is more plausible than the three nonsignificant ones. Using cumulative quartz exposure, the slope is flat with no suggestion of a trend. The authors conclude there is no E-R relationship, and the untransformed cumulative exposure metric is considered the more appropriate variable. The South African studies have considerable overlap in subjects. The E-R trends are significant in Hnizdo and Sluis-Cremer (1991) and marginally nonsignificant in Reid and Sluis-Cremer (1996) and Hnizdo et al. (1997). Hnizdo and Sluis-Cremer (1991) and Hnizdo et al. (1997) are from the same cohort, the cases are the same subjects, and they appear to be a subset of the subjects in Reid and Sluis-Cremer (1996). Greater weight is given to Reid and Sluis-Cremer (1996) because of the larger sample size, wider age range, and longer follow-up. In sum, there is one study (Reid and Sluis-Cremer, 1996) with a marginally nonsignificant E-R trend and one study (de Klerk and Musk, 1998) with a flat E-R curve showing no association at all.

None of the other studies in Figure 1 is suggestive of a biological gradient based on quantitative estimates of exposure. To the contrary, the preponderance of the studies consistently shows no E-R trend. These studies do not support the silica/lung cancer hypothesis.

2. The Silicosis/Lung Cancer Hypothesis

Figure 3 visually displays the results of four studies evaluating lung cancer risk rates among silicotics by severity of silicosis. The four studies are evenly divided: Two of the studies

(Hessel et al., 1986; Dong et al., 1995) show a trend for the risk of lung cancer to increase as severity of silicosis increases (though the trend is not statistically significant in Hessel, et al, 1986). Two of the studies (Hessel et al., 1990; Carta, et al., 1991) show a trend for lung cancer risk to decrease as severity of silicosis increases. All the studies are adjusted for smoking except the Chinese refractory brick workers (Dong et al., 1995).

Figure 3 also shows the four studies that have assessed the risk of lung cancer among silicotics by dust exposure. Three show decreasing risk with increasing exposure (Hessel et al., 1986 (autopsy); Hessel et al., 1986 (radiological); Hessel et al., 1990). The third (Carta et al., 1991) shows RRs of approximately 2 for the medium and high exposure categories as compared to the low exposure category, but the 95% confidence intervals are below 0.5. Moreover, the apparent increase in risk with increasing dust exposure in Carta et al. (1991) is inconsistent with the analysis by severity of grade of silicosis, since Category 2 and Category 3 silicotics in that study show lung cancer RRs <1 compared to Category 1 silicotics.

These data do not provide support for the silicosis/lung cancer hypothesis.

D. Consistency

IARC (1997) explains the criterion of consistency as follows: "Associations that are replicated in several studies of the same design or using different epidemiological approaches or under different circumstances of exposure are more likely to represent a causal relationship than isolated observations from single studies."

1. The Silica/Lung Cancer Hypothesis

The potential association of silica exposures and lung cancer has been investigated in a number of different industries, in a number of different countries, by authors using a number of different approaches. As discussed above and reflected in Figure 1 and Table 3, results from more than a dozen comparisons are available that also provide quantitative estimates of silica exposure and analyses of E-R trends. These studies show no consistent association between increasing silica exposure and increased risk of lung cancer. To the contrary, of the twelve studies listed in Table 3 involving exposure to quartz, only one (Hnizdo and Sluis-Cremer, 1991) shows a statistically significant association, and that association was no longer significant when an adjustment for silicosis was made in a follow-up study of the same cohort. (Hnizdo, et al., 1997). Thus, there is a consistent pattern of no significant association with lung cancer in studies of quartz-exposed workers.

The remaining two studies in Table 3 -- U.K. pottery workers studied by Cherry et al. (1997) and U.S. diatomaceous earth workers studied by Checkoway et al. (1997) -- could be read to suggest that exposure to cristobalite may increase the risk of lung cancer. But there were no measurements of cristobalite exposure in the U.K. pottery study, so the link with cristobalite is

somewhat tenuous, and the 90% confidence intervals used to evaluate the data in that study make it difficult to know whether the findings reflect a chance occurrence. While there was a possible marginally increased lung cancer risk among the highest exposed diatomaceous earth workers in Checkoway et al. (1997), the results in that study may have been confounded by exposure to asbestos and by possible misclassification of silica exposure among pre-1930 hires.

Given these limited and uncertain data, one cannot say there is a consistent association between cristobalite exposure and lung cancer. Instead, that hypothesis remains indeterminate.

2. The Silicosis/Lung Cancer Hypothesis

The results of studies of silicotics meeting the criteria for inclusion in a weight-of-evidence analysis are summarized in Figures 2 and 3 and Table 4. With very limited exceptions, when the presence or severity of silicosis is used as the relevant metric, the data show a pattern of no significant difference in risk for silicotics compared to nonsilicotics or for persons with more severe grades of silicosis compared to persons with less severe grades. These studies are largely unconfounded by smoking or exposure to occupational carcinogens, and they are not biased by incomplete enumeration or a diagnosis influenced by smoking-related symptoms. The data clearly do not show a consistent association of silicosis with increased cancer risk and, therefore, detract from the silicosis/lung cancer hypothesis.

E. Coherence

Coherence is the idea that all the pieces should fit together and be compatible with the hypothetical relationship being tested, *i.e.*, that silica exposure or silicosis increases the risk of lung cancer. If silica is a carcinogen, one would predict several coherent outcomes. To the extent the predictions coincide with fact, the hypothesis is supported. Conversely, if the predicted outcomes have not been observed, there is a lack of coherence that detracts from the hypothesis. Coherence is, in part, a summary of previous criteria such as strength of association and E-R, as these relationships are among the predicted outcomes in a coherent body of evidence.

Among the outcomes that one would expect to find if the silica/lung cancer hypothesis had coherence are the following.

- There should be a consistent association between lung cancer risk and increasing exposure to silica. As discussed above, the preponderance of studies of silica-exposed workers do not show an association between increasing silica exposure and increasing risk of lung cancer. Where associations have been found at all, they are weak and, in almost all cases, not statistically significant. This is not the kind of coherence one would expect if a true causal association existed -- particularly when these findings are contrasted with the strong associations between increasing silica exposure and NMRD found in many of these same cohorts.

- The highest and most consistent risk should be among silicotics. Studies of silicotics are analogous to a worst case situation, as silicotics generally have had high exposure and/or are highly susceptible to silica, and they have experienced a potentially adverse effect caused by silica exposure. Thus, if silica exposure increases the risk of lung cancer, the coherence criterion would predict that silicotics will be at highest risk, and the risk should increase as severity of silicosis increases. As discussed above and shown in Table 4 and Figures 2 and 3, this is not the case. Instead, as Figure 2 indicates, silicotics do not show a consistently increased risk of lung cancer in relatively unbiased and unconfounded studies. Similarly, as shown in Figure 3, the four studies that evaluated the association of lung cancer with severity of silicosis are evenly split, and in the two studies where lung cancer risks are greater among those with more severe grades of silicosis, the trend is not significant in one and of questionable significance in the other.

- The findings in a series of necropsy studies conducted prior to the 1950's in several different countries and with quite a large number of post-mortem autopsies are congruent with the data summarized in the previous two paragraphs. Summarizing the reports by Meiklejohn (1949a,b) of pottery and sandstone workers in the U.K. and other studies (including some from South Africa), Heppleston (1985) concluded that "primary carcinoma of the lung shows no demonstrable causal connection...with the prior existence of pneumoconiosis." The data are summarized in the following chart:

		Percent lung cancer at Necropsy		
Study Population	N	Silicosis	No Silicosis	No silicosis, no silica exposure
UK Pottery Workers (1932-1948)	750	3.6%	7.3%	0.8%
UK Sandstone Workers (1932-1948)	275	1.9	9.2	--
South African Gold Miners 1920-1938	6046	0.72	0.74	1.3
1948-1951	1300	3.6	4.1	--
Age 45-65	800	~8	~8	--

These data do not support the hypothesis that silicotics are more prone to contract lung cancer. Although these comparisons are not adjusted for differences in age or smoking, the differences in prevalence, as Heppleston (1985) points out, would likely increase even further if such adjustments were to be made. While lung cancer was relatively rare, the autopsy is likely to have discovered even incipient cases that would likely be missed without an autopsy.

- If silica is a carcinogen, one would expect the quartz content of the lung to show a dose-response trend; that is the quartz content should increase as one goes from persons without silicosis or lung cancer, to persons with silicosis but without lung cancer, to persons with both silicosis and lung cancer. Loosereewanich et al. (1995) analyzed lung silica concentrations in nine silicotic gold miners with lung cancer, 22 noncancer silicotic gold miners, and 10 victims of accidental deaths. The geometric mean (GM) silica concentrations were 2.5 million, 4.3 million, and 0.34 million particles/mg of dried lung tissue respectively. The noncancer silicotics had higher, but not statistically significant, mean concentrations of quartz in the lung than did the silicotics with lung cancer. While confounding exposures such as smoking and radon were not taken into account in this study and the number of subjects is quite small, the authors concluded that the data "do not provide support for the hypothesis of a relationship between silica exposure and lung cancer."

As the foregoing points illustrate, the outcomes that one would expect to find if the silica/lung cancer hypothesis had coherence are not observed.

F. Biological Plausibility

Biological plausibility is an important criterion for evaluating causality, especially when the epidemiological evidence is inconsistent and the association is weak. Biological plausibility will not be discussed in this Review, but a few observations should be made. IARC concluded there was sufficient evidence in experimental animals for the carcinogenicity of quartz. This conclusion was based in part on four inhalation studies and four studies of intratracheal instillation in rats which produced lung tumors. However, the rat is not an appropriate model for humans because the rat develops lung tumors without reduced lifespan from a wide variety of both carcinogenic and noncarcinogenic substances. By contrast, there was no increase in tumors in any other tested animal species -- including the mouse, guinea pig, and Syrian hamster -- even though some tested animals, such as the A-strain mouse, are notably susceptible to the induction of lung tumors. Thus, on balance, one must conclude that consideration of biological plausibility has, at best, an indeterminate effect on the silica/lung cancer hypothesis.

G. Summary

Applying the Bradford Hill criteria, we find that the weight of the evidence does not support a causal association between silica exposure and lung cancer or between silicosis and lung cancer.

- The strength of association, where it exists at all, is weak and, in almost no case is it statistically significant even though most studies have adequate statistical power.

- An E-R relationship between increasing silica exposure and lung cancer is usually absent -- in sharp contrast to the strong E-R relationships observed with nonmalignant respiratory disease in many of the same cohorts.

- There are no convincing dose-response relationships with lung cancer where silicosis is used as a surrogate for dose.

Overall, among studies that are relatively free of confounding and bias, the weight of the evidence does not support a causal association either between silica exposure and lung cancer or between silicosis and lung cancer.

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TABLE 1

STUDIES FOR TESTING THE SILICA/LUNG CANCER HYPOTHESIS

STUDY POPULATION	QUANTITATIVE E-R ANALYSIS	CONFOUNDING/BIAS	DESIGN
CATEGORY ONE: COHORTS THAT MEET THE CRITERIA			
Gold Miners			
South Africa			
Hessel et al. (1990)	Yes	No/No	Nested case-control
Hessel et al. (1986)	Yes	No/No	Nested case-control
Reid and Sluis-Cremer (1996)	Yes	No/No	Nested case-control
Hnizdo and Sluis-Cremer (1991)*	Yes	Radon?/No	Nested case-control
Hnizdo et al. (1997)			Nested case-control
United States			
Steenland and Brown (1995)	Yes	Smoking?/No	Nested case control; reported mostly on cohort results
Australia			
de Klerk and Musk (1998)	Yes	No/No	Nested case-control
Metal Miners			
China			
McLaughlin et al. (1992)			
Tungsten	Yes	No/No	Nested case-control
Iron-Copper	Yes	No/No	Nested case-control
Potteries			
China			
McLaughlin et al. (1992)	Yes	PAH (slight)/No	Nested case-control
United Kingdom			
Cherry et al. (1997)	Yes	No/No	Nested case-control
Diatomaceous Earth			
Checkoway et al. (1997)	Yes	Smoking; asbestos/No	Cohort (SRR) (internal analysis)
Foundry Workers			
Andjelkovich et al. (1994)	Yes	No/No	Nested case-control
CATEGORY TWO: EXCLUDED COHORTS THAT DO NOT MEET THE CRITERIA			
Refractory Brick			
Italy			
Merlo et al. (1991)	No (latency by tenure only)	Smoking/external referent only	Cohort (SMR)
China			
Dong et al. (1995)	No (latency only)	Smoking/external referent only	Cohort (SRR)
Granite/Crushed Stone			
Vermont Granite Sheds			
Costello and Graham (1988)	No (latency by tenure only)	Smoking/external referent only	Cohort (SMR)
United States Crushed Stone			
Costello et al. (1995)	No (latency by tenure only)	Smoking/external referent only	Cohort (SMR)
Danish Stone Cutters			
Guenel et al. (1989b)	No (no latency or tenure)	Smoking/incomplete enumeration	Cohort (SIR)

* Same cases in Hnizdo and Sluis-Cremer (1991) and Hnizdo et al. (1997), and is a subset of Reid and Sluis-Cremer (1996)

TABLE 2

STUDIES FOR TESTING THE SILICOSIS/LUNG CANCER HYPOTHESIS

STUDY POPULATION	SILICOSIS DIAGNOSIS	QUANTITATIVE E-R	CONFOUNDING/ BIAS	DESIGN
CATEGORY ONE: COHORTS THAT MEET THE CRITERIA				
Hessel et al. (1990), South African Gold Miners	Autopsy (parenchymal & pleural)	Yes	No/No	Nested case-control
Hessel et al. (1986), South African Gold Miners	Autopsy (parenchymal & pleural)	Yes	No/No	Nested case-control
Hessel et al. (1986)	Radiological	Yes	No/No	
Hnizdo and Sluis-Cremer (1991)*	Autopsy	Yes	Radon?/No	Nested case-control
Hnizdo et al. (1997), South African Gold Miners	Radiology (≥ 1/1)	No	Radon?/No	Nested case-control
Cherry et al. (1995), U.K. Potteries	Radiology (≥1/0)	No	No/No	Nested case-control
Carta et al. (1991), Sardinia Dusty Trades	Radiology (≥1/0)	Yes	No/No	Nested case-control
McLaughlin et al. (1992), China				
Potteries	Radiology (Chinese)	No	PAH?/Enumeration?	Nested case-control
Tungsten Mines	Radiology (Chinese)	No	No/Enumeration?	Nested case-control
Iron-Copper Mines	Radiology (Chinese)	No	No/Enumeration?	Nested case-control
Dong et al. (1995), China Refractory Brick	Radiology (Chinese)	No	Smoking?/ Enumeration?	Cohort (SRR)
CATEGORY TWO: COHORTS THAT DO NOT MEET THE CRITERIA				
Amandus et al. (1992), North Carolina Dusty Trades	Reclassified radiology (≥1/0)	No	Smoking/ Enumeration	Cohort (SMR) of silicotics
Partanen et al. (1994), Finnish Silicotics	Compensation radiology	No	Other carcinogens/ Compensation diagnosis, enumeration	Cohort (SIR)) of silicotics
de Klerk and Musk (1998), Australian Gold Miners	Compensation radiology	No	No/Compensation diagnosis	Nested case-control

* Same subset of South African gold miners with lung cancer

TABLE 3

RESULTS FROM STUDIES OF SILICA-EXPOSED WORKERS REGARDING STRENGTH OF ASSOCIATION AND BIOLOGICAL GRADIENT

STUDY	STRENGTH OF ASSOCIATION*	BIOLOGICAL GRADIENT (E-R)
Hypothesis: Does exposure to silica increase the risk of lung cancer?		
Gold Miners		
Hessel et al. (1990)	No association	No trend
Hessel et al. (1986)	No association	No trend
Reid and Sluis-Cremer (1996)[+]	Weak association	Marginally nonsignificant trend
Hnizdo and Sluis-Cremer (1991)[++]	2.92-fold increase ($p < 0.01$)	Significant trend ($p < 0.01$)
Hnizdo et al. (1997)	Weak association	Marginally nonsignificant trend
Steenland and Brown (1995)	No association	No trend
de Klerk and Musk (1998)	No association	No trend
Other Miners		
Tungsten		
McLaughlin et al. (1992)	No association	Inverse trend ($p < 0.01$)
Iron-Copper		
McLaughlin et al. (1992)	No association	Inverse trend ($p > 0.05$)
Potteries		
McLaughlin et al.(1992)	Weak association	Nonsignificant trend ($p > 0.05$)
Cherry et al. (1997)	No association	Inverse trend
Iron Foundry Workers		
Andjelkovich et al. (1994)	No association	Inverse trend
Possible Cristobalite Exposure		
U.K. Pottery		
Cherry et al. (1997)	Weak association (significant)	Not evaluated: assessed only ever versus never exposed
Diatomaceous Earth		
Checkoway et al. (1997)		
Regression adjustment for asbestos	Weak association (significant)	Marginally significant trend
Exposed to silica but not asbestos by authors' classification	Weak association	Only elevated RR is in high exposed category

* Weak association = RR about 2 or less in high exposed category; association is not significant unless otherwise noted

No association = RR about 1 in high exposed category; association is not significant unless otherwise noted

[+] Hnizdo and Sluis-Cremer (1991) is a subset of Reid and Sluis-Cremer (1996)

[++] Same lung cancer cases in Hnizdo and Sluis-Cremer (1991) and Hnizdo et al. (1997); >41,000 particle-years to start of follow-up in Hnizdo and Sluis-Cremer (1991)

TABLE 4

RESULTS FROM STUDIES OF SILICOTICS REGARDING STRENGTH OF ASSOCIATION AND BIOLOGICAL GRADIENT

STUDY	STRENGTH OF ASSOCIATION*	BIOLOGICAL GRADIENT	
		DOSE-RESPONSE** (severity of silicosis)	EXPOSURE-RESPONSE***
Hypothesis: Are silicotics at Increased Risk of Lung Cancer?			
Hessel et al. (1990) (autopsy)	No association	Inverse trend ($p = 0.76$)	Inverse trend
Hessel et al. (1986) (autopsy)+	Weak association	Nonsignificant trend ($p = 0.08$)	Inverse trend
Hessel et al. (1986) (radiology)	No association	–	Inverse trend
Hnizdo and Sluis-Cremer (1991) (autopsy)++	No association	–	–
Hnizdo et al. (1997) (radiology)	Weak association	–	–
Cherry et al. (1995) (radiology)	Weak association	–	–
Carta et al. (1991) (radiology)	No association+++	Nonsignificant Inverse trend	Nonsignificant trend
McLaughlin (1992) (radiology)			
Potteries	No association	–	–
Tungsten Mines	No association	–	–
Iron-Copper Mines	3.1-fold increase ($p < 0.05$)	–	–
Dong et al. (1995) (radiology)	2.5-fold increase (nonsignificant)	Increasing trend	–

* Weak association = RR about 2 in silicotics compared to nonsilicotics; association is not statistically significant unless noted otherwise
No association = RR about 1 in silicotics compared to nonsilicotics; association is not statistically significant unless noted otherwise

** Dose-response means assessment of risk by severity of silicosis

*** E-R means assessment of risk among silicotics by silica exposure

\+ Same cases and controls in radiological/autopsy analysis of Hessel et al. (1986)

++ Same lung cancer cases in Hnizdo and Sluis-Cremer (1991) and Hnizdo et al. (1997)

+++ SMR based on comparison of silicotics to expected rates for the regional population

Figure 1: Exposure-Response: Lung Cancer with Quantitative Estimates of Cumulative Silica Exposure

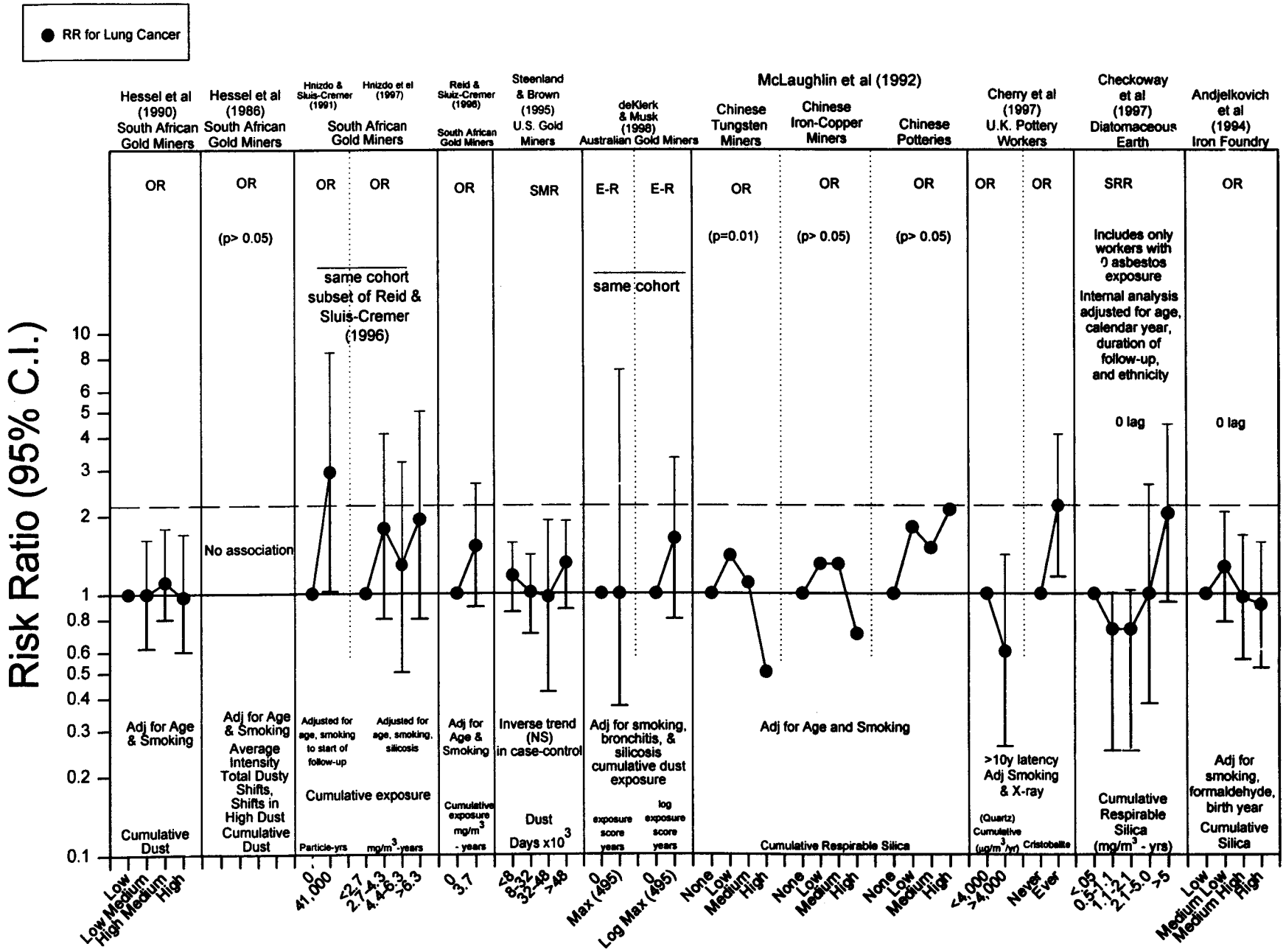


Figure 2: Risk of Lung Cancer: Comparison of Silicotics versus Non-Silicotics: Test of Silicosis/Lung Cancer Hypothesis

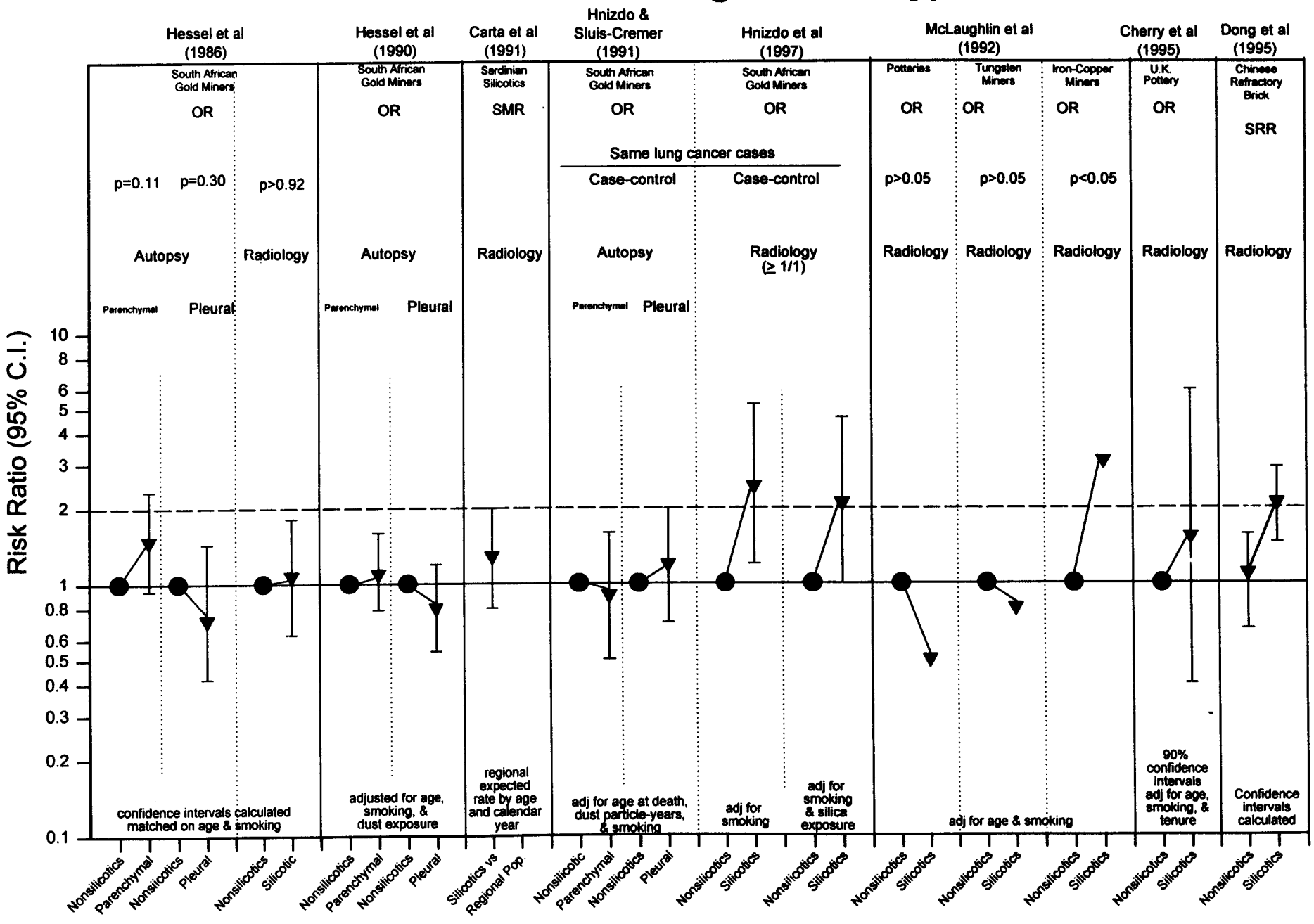
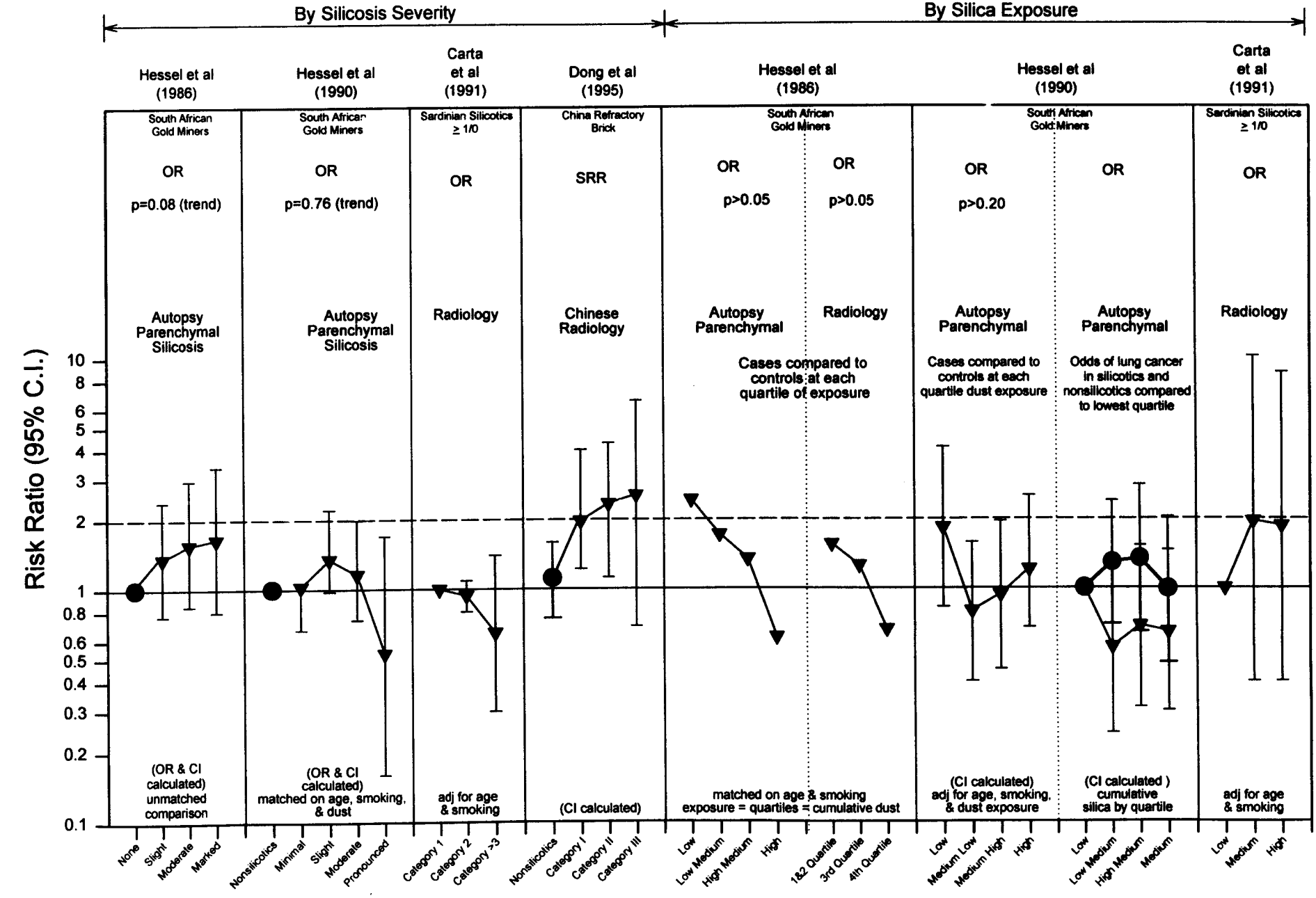


Figure 3: Risk of Lung Cancer Among Silicotics by Severity of Silicosis and by Exposure: Test of Silicosis/Lung Cancer Hypothesis



CRYSTALLINE SILICA AND CANCER

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EXECUTIVE SUMMARY

ANIMAL STUDIES

There can be no question that lung tumors have occurred in rats following exposure to crystalline silica by a variety of techniques. However, no other species has exhibited the same response and there is a strong possibility that the carcinogenic response in the rat is a specific and even unique phenomenon peculiar to that species. This possibility is supported by a number of facts: no dose response has been identified; in most, if not all, positive studies, large "overload" doses have been used; strains of other species considered especially sensitive to pulmonary carcinogens have been uniformly negative; when subjected to high dose inhalation of several nuisance dusts, rats have been shown to be susceptible to changes in lung epithelial cells not always exhibited by other species. In addition, female rats seem to be more susceptible to silica induced carcinogenesis. In every study where tumors have been observed, fibrosis has also been present; conversely, in other species no tumors have been seen even when fibrosis was present.

MECHANISTIC STUDIES

Many of the most common in vitro assays for mutagenesis and potential carcinogenesis (NB., not all mutagens are carcinogens) are either negative or insensitive when crystalline silica is the test subject: silica particles are not mutagenic in the so-called Ames bacterial assays; the Syrian hamster embryo (SHE) bioassay has been generally negative. Some in vitro assays have shown equivocal results: sister chromatid exchange (SCE) assays using co-cultures of human lymphocytes and monocytes were positive with very high doses of tridymite but Min-U-Sil tested negatively in this system and in Chinese hamster ovary (CHO) cells. One tranformation assay using mouse fibroblasts has been positive but dose response differences were not straightforward, data is unpublished and neither negative nor positive control dusts were apparently used. Cell proliferation assays indicate similar responses to crystalline silica by epithelial cells and fibroblasts which may suggest a functional or causal relationship between fibrosis and carcinogenesis. By extension, this raises the possibility of fibrosis being a necessary factor if lung tumors are to occur after this type of exposure. This also supports the possibility of a threshold being identifiable in the one species where tumors have been observed.

CONCLUSIONS

- Only one species (the rat) has exhibited a tumorigenic response. The rat may possess a unique sensitivity to many nuisance or "inert" dusts.

- All other species tested, including some highly sensitive strains, have been negative.

- In the rat there appears to be a gender-related susceptibility to tumor occurrence.

- No useful dose response data exist in any single study nor when comparisons are made among studies using similar exposure methods.

- Lung overload phenomena, as yet only poorly understood, may be a determining factor in the positive rat studies.

- Fibrosis has been observed in the lungs of all animals developing tumors.

- Most common mutagenesis assays are negative or insensitive to silica induced changes.

- Changes observed in <u>in vitro</u> systems, when they have occurred, have been equivocal at best and usually have resulted after extremely high doses.

- Cell proliferation assays suggest a functional or causal relationship between fibrosis and carcinogenesis; further raising the possibility of a threshold in sensitive species.

Animal Studies

As early as 1983 reports of quartz-induced lung cancer in one species of laboratory rodents began to appear in the literature. Subsequent reports dealt with exposure of several species by two principal methods: inhalation and direct intratracheal instillation. Among the rodents tested only the rat has exhibited a neoplastic response. Prior to this time a number of studies were reported in which the exposure methods were much less comparable to the natural exposures that can be anticipated in either industrial or public environments. Examples of the latter are intrathoracic injection into the lung parachyma of rabbits (Kahlau, 1961) or injection of test material into the intrapleural space (Wagner, 1970; 1976). Too little information on the rabbit experiments (e.g., age, sex, condition, degree of surgical interference, etc.) is available to be useful. The intrapleural experiments, performed on rats, gave rise to neoplasms of an unusual type that appeared to be specific to the pleural tissues. The resulting tumors may be as much related to experimental method as to the potential carcinogenicity of the materials involved. Nothing in the literature suggests that the crystalline silicas commonly deposit in the pleural areas following inhalation.

Several issues stand out among the more recent experiments: only one species (the rat) has shown positive results; the appearance of tumors is a late phenomenon; lung fibrosis is usually present in tumor bearing animals; conversely, not all species exhibiting fibrosis exhibit tumors. In addition, there are no true dose response studies reported from one laboratory where identical methods of exposure were used. Even among the more recent intratracheal and inhalation studies, differences in method, and in some cases materials, exist.

Intratracheal Exposure

This method involves intubation of the trachea, usually during short term anesthesia, and the injection of the test material suspended in a physiological solution. In some experiments the intubation is manipulated to allow delivery into a specific lung lobe. In rodents, because the total lung volume is small, the doses administered are usually of small volume. Larger total doses are achieved by repetitive instillation over a longer period (e.g., 1x/wk for n wk.) Most studies have employed either a relatively large single dose or multiple (usually weekly) doses with all or a portion of the animals followed for lifetime. The ability to deliver an exact dose at a precise anatomical location and to expose a single lobe are some of the advantages to this method. It is also less expensive than most inhalation approaches.

Both Syrian hamsters and female Sprague-Dawley rats were used in parallel experiments at Los Alamos for intratracheal studies of Min-U-Sil. The rats were exposed to 7mg of Min-U-Sil suspended in 0.2 ml of saline weekly for ten weeks and were allowed to complete their lifespans without sacrifice. The hamster studies were

the same except for the addition of a group exposed to 3 mg on the same schedule. Among rats, interstitial and some nodular fibrosis was observed. Five of the rats developed carcinomas and one exhibited an adenoma (16%). All of the rats developing lung tumors also developed marked fibrosis. None of the hamsters in either group developed lung tumors and few developed recognizable fibrosis. The only treatment related lesion appeared to be a mild pneumonitis in a few animals (Holland et. al., 1983).

Renne and his colleagues reported on a dose response study using Syrian hamsters in which Min-U-Sil was administered by the intratracheal route. Groups of 25 hamsters received either 0.03, 0.33, 3.3 or 6.0 mg of quartz each week for 15 weeks and four other groups of animals were given ferric oxide along with the quartz treatment. No pulmonary tumors were reported in any group. The authors observed a dose-related septal fibrosis which was described as slight. There was no apparent enhancement attributable to the addition of ferric oxide to the quartz exposures. (Renne et. al., 1985).

Groth and his colleagues exposed Fischer 344 rats to one of two varieties of quartz using intratracheal administration of a single 20 mg dose. The intubation procedure was performed so that all test materials were deposited in the left lung. The silica products were Min-U-Sil (a quartz product with a particle size of 5 microns or less) and Novaculite (a silica-bearing mineral) (Groth et. al., 1986). By the time the experiments were completed, the Novaculite group exhibited a 29% lung tumor incidence and the Min-U-Sil exposed animals exhibited a 45% incidence. With the exception of one epidermoid carcinoma seen in a Novaculite-exposed animal, all tumors were described as adenocarcinomas. Several of the adenocarcinomas were reported to have arisen in, or as being associated with dense scars. Several different types of fibrosis were described including some nodular or silicotic fibrosis which apparently occurred only in animals with no tumors. Most tumors were found in the exposed (left) lung but several were found in the right lung as well. The authors reported that in the early sacrifices, the granulomas and fibrotic changes were restricted largely to the left lung (the original installation site) but later in the experiment the right or unexposed lung became increasingly involved. The report also provided comprehensive descriptions of the exposure materials including elemental trace analysis and determination of the comparative surface areas for each material. The surface area of Min-U-Sil (4.3 m^2/g) was more than twice that of Novaculite (1.6 m^2/g.) (Groth et. al., 1986).

Saffiotti and his colleagues (Saffiotti et all 1988, 1990, 1992) reported on a studies in which both male and female F344 rats were given single IT installations of 12 mg quartz as Min-U-Sil or hydrofluoric (HF) acid etched Min-U-Sil. The experiments achieved cumulative tumor rates as high as 89% in some groups after 26 months. The HF treatment was done as an attempt to remove surface impurities which might affect the production of reactive oxygen at the particle surface. The HF etching

treatment did not appear to effect tumor incidence. This is the highest rate of tumor production yet reported in experimental animals.

Inhalation Exposure

This exposure method is the most physiologically correct way of exposing animals to dusts or liquid aerosols for either long-term or short-term studies. Because the animals inhale the test material in a natural way, the entire respiratory tract, including the nares, pharynx and trachea are exposed. In most experiments, where the animal subjects are continually housed in the exposure chamber, there is also exposure of the whole body including oral cavity, skin, hair and eyes. Whole body exposure raised several issues (e.g., non-respiratory effects, resuspension of aerosols from the hair) that are probably not of great importance to the subject at hand. The nose-only method avoids general exposure of the skin and hair but requires mild restraint of the animal during the exposure period. Either method does not allow the precise definition of deposited dose afforded by intratracheal installation.

Wilson and coworkers used inhalation to expose BALB/c mice to Min-U-Sil in a long term study (Wilson et. al., 1986). They used a total of sixty mice divided into smaller subgroups which were exposed for either 6 months, one year or two years at particle concentrations ranging from about 1500 to 2000 $\mu g/m^3$. Included in the study was an equal number of unexposed controls that were sacrificed on a schedule matched to that of the test animals. The BALB/c strain has a moderate background of lung adenoma, and while the quartz exposed animals developed adenomas, the incidence was not different from that of the control group. No carcinomas were observed. It should be noted that the concentration expressed here as 2000 $\mu g/m^3$ ($2mg/m^3$) was not unlike the $1mg/m^3$ used by Muhle in rats (Muhle et. al. 1989 see below). In general terms, the mouse has a body weight in the neighborhood of 10% of the F344 rat and if lung weights scale at approximately the same proportions, the dose delivered in Wilson's mouse experiments was at least equivalent to the Muhle rat studies.

In an inhalation study of female and male F344 rats Dagle (Dagle et. al. 1986) used a concentration of $50mg/m^3$ of Min-U-Sil. The exposures were performed 6h/day on 5 days each week for 24 months. The chambers allowed a whole body exposure. Dust was generated using a dry flexible-brush technique. Seventy two rats of each sex were initially exposed; however, 10 animals of each sex were removed from exposure at four, eight, twelve and sixteen months with the remaining rats continuing to be exposed until 24 months had passed. At each intervention, half of the animals were sacrificed for pathology and the remaining half were retained without further exposure. All survivors were sacrificed at 24 months. A sham control group sacrificed on the same schedule was reported. The overall tumor

incidence was 12%. When the incidence was analyzed according to gender, the females experienced a much higher rate (19%) than the males (2%). Three of the 10 tumors seen in females developed in animals that lived 24 months but were retired from exposure at four months. All tumors observed in this study were of the epidermoid type. The authors also reported lipoproteinosis, metaplasia of alveolar epithelium, septal thickening and nodular fibrosis in most of the exposed animals.

Sixty two female Fischer-344 rats were used in long term inhalation studies by Holland (Holland et. al. 1986). In this study the animals were exposed to concentrations of 12 mg/m^3 of Min-U-Sil for 6 hr/day on 4 days/week for 83 weeks. A nose-only method of exposure was used allowing all 62 animals to be exposed in the same chamber. The quartz-dust was produced by compressed air nebulization of a liquid suspension of quartz. The particle-containing droplets thus formed were passed through a drying chamber and charge neutralized prior to entering the exposure chamber. Sixty two sham control animals were exposed to filtered air by the same methods and another group of 15 were used as unmanipulated controls. Of 60 quartz-exposed rats examined histopathologically, 18 developed lung tumors (30%). The first tumor was observed after 17 months of exposure and some animals developed more than one tumor. Of the 20 tumors observed in 18 animals, six were benign adenomas and 14 were carcinomas: 3 squamous (epidermoid) carcinomas and 11 adenocarcinomas. The histological material from this study was further examined using electron microscopy and it was reported that the adenocarcinomas originated from Type II alveolar cells. The cell type from which the squamous tumors arose could not be determined (Johnson et. al., 1987). Most animals living beyond 400 days developed lipoproteinosis, granulomas, granulomatous lymphadenopathy, some interstitial fibrosis, some discrete nodular fibrosis and granulomatous plaques involving the pleura.

In a study comparing the fibrogenic effects of SiO_2 and TiO_2, Muhle and colleagues (1992) have reported a tumorigenic response by F344 rats to exposures of only 1 mg/m^3 of quartz (DQ-12) of which 74% was of respirable size. One hundred rats (50 of each sex) were exposed in horizontal flow whole-body chambers for 6hr/day, 5 days/week for 24 months using a dry aerosol technique. Parallel groups were exposed to titanium dusts or to air only. The animals developed extensive subpleural and peribronchiolar fibrosis which the authors report as unlike the nodular fibrosis seen in human silicosis. The lung collagen content was more than doubled as was the lung weight. The authors also report a mean retained particle mass of 0.91 mg/lung for the quartz exposed animals (compared to a mean of 2.72 mg/lung for the TiO_2 exposed animals). Tumors were first observed after 21 months of exposure. Eighteen of the quartz exposed animals developed lung neoplasms of which 12 were reported as malignant. Most of the malignant tumors were adenocarcinomas (10). They also observed two adenomas and four keratinizing cystic squamous cell tumors which they regarded as benign. In the quartz exposed group, the overall tumor incidence (both

benign and malignant) involved more females (12) than males (6). (Muhle et. al., 1989).

In a study of the effects of colloidal ^{232} ThO_2 (Thorotrast) and quartz (DQ 12), Spiethoff (Spiethoff et. al. 1992) reported lung tumor incidences of 52% and 45% respectively in two groups of female Wistar rats exposed to quartz by nose only inhalation. The high dose group comprised animals exposed to 30mg/m^3 for 6h/day on 5d/week for a total of 29 days. The lower dose group was exposed to 6mg/m^3 on the same schedule. In this study squamous cell carcinomas were found somewhat more frequently than adenocarcinomas in animals exposed to quartz alone. Additional groups of animals were intravenously injected with Thorotrast following inhalation exposure to quartz. The lung tumor incidence in the two groups exposed to quartz and Thorotrast was 67% and 44%, respectively. Animals exposed to Thorotrast alone had only a 3% incidence of lung tumors. There was no question that the lung tumor incidence in Thorotrast/quartz exposed animals indicated at least an additive effect. While this study included intervening sacrifices, many animals in each group were allowed to live for 24 months, and the first tumor was not observed until one year into the experiment.

The preneoplastic and neoplastic lesions developing in rats after inhalation of silica consist of many adenomas and adenomatosis, as well as squamous metaplasia. These lesions are benign and uncommon in man, and may occur as nonspecific cellular responses to a number of inhaled foreign particulates (Craighead 1990, 1992). Peripheral alveolar carcinomas are the most common type of fibrosis-associated tumors induced by silica in the rat model whereas the incidence of bronchoalveolar tumors is less than 5% of total lung cancers observed in man. Unfortunately, detailed descriptions of rat adenocarcinomas and other differentiated tumors are not provided in many papers by pathologists, and the malignancy of documented lesions often was not ascertained by injection of tumors into nude mice or syngeneic animals.

SUMMARY OF ANIMAL STUDIES AND UNANSWERED QUESTIONS

Recent animal experiments indicate that the most common strains of laboratory rats are susceptible to pulmonary tumor induction when exposed to crystalline silica, One exception is a recently reported inhalation study (Rosenbruch et al., 1990) in which Wistar rats were exposed to 10 mg/m3 for 7h/day on 5 days each week for 12 months. Some animals were allowed to live an additional 12 months. While severe fibrosis was observed, no tumors were reported.

Treatment technique, i.e. inhalation vs. intratracheal exposure, does not appear to be a determining factor. Some intratracheal experiments used only a single dose (experiments by Saffiotti and Groth), while others used multiple doses (experiments by Holland and Renne). In the inhalation experiments, both short-term exposure

(Dagle, Speithoff) and quasi-lifetime exposure (Dagle, Holland, Muhle) induced tumors.

Crystalline silica has not induced lung tumors in any other species reported in the literature, These species include the Syrian hamster (Holland, Renne Saffiotti studies), the mouse (Wilson, Saffiotti studies) and the Guinea pig (Pratt, 1983). Saffiotti used the A strain mouse which is susceptible to lung tumors by other agents. In the Guinea pig experiment, the object was to study dose retention. In this instance, cristobalite silica was used in a long term inhalation study and the author reports that the lung tissue was examined. While fibrosis was apparently induced,no tumors were reported (Pratt, 1983).

Obvious questions are raised by these results: Is there a specific unique susceptibility among laboratory rats to silica and/or other dusts inducing lung tumors? For example, a recent chronic NTP study indicated lung tumors in rats, but not mice, after inhalation of talc, and this trend in species specificity is observed with a number of other inert or nuisance dusts. Is susceptibility gender related? At least some experiments with silica suggest an increased susceptibility in the female rat (Dagle, Muhle), and this appears to be true in talc, volcanic ash, titanium dioxide and other chronic particle inhalation studies (Boorman, G., presentation at A Workshop- "Talc: Consumer Uses and Health Perspectives", The International Society of Regulatory Toxicology and Pharmacology and The United States Food and Drug Administration, NIH, Bethesda, MD, 1994). Is fibrosis necessary for tumor induction by contributing to changes in pulmonary cell populations, altering dose deposition/retention phenomena, or by other mechanisms? For example, crystalline silica appears to clear slowly from the lung, and it has been observed that the slow clearance may be related to cellular toxicity rather than excessive lung burden (Bellman, 1991). In experiments dealing with radioactive materials and quartz there appears to be agreement that pre-existing fibrosis did not influence tumor induction (Spiethoff and Lundgren studies). In both instances, however, the radiation insult was administered after the fibrosis was established, and the insults were consecutive rather than parallel.

Most reported experiments have involved relatively high doses of the crystalline silica materials. This is typical of inhalation studies which have yielded tumors in rats using a variety of both carcinogenic (i.e. asbestos) and noncarcinogenic (titanium dioxide, carbon black) particles in man. These experiments have been performed at airborne concentrations of > 1 mg/m3 air, concentrations which result in lung "overload" as documented by an inflammatory response or impairment of normal defense mechanisms (Health Effects Institute, 1991). One exception is the work of Muhle (1989) where a respirable concentration below 1 mg/m3 was used. With one exception (Spiethoff, 1992), multiple dose experiments in the rat have not been reported, and no true dose response has been established. Spiethoff did report two dose levels, but the tumor induction rates were not that different. It should be

emphasized that the positive inhalation studies in rats have been chronic, high-dose exposures, and although "peak" or transient exposures to silica dusts at comparable levels might occur in the workplace, these brief exposures would not be expected to result in cumulative exposures of dusts high enough to achieve tumors as demonstrated in rat inhalation models.

It should also be noted that the induction of lung tumors in experimentally exposed animals is a recent phenomenon, i.e. most reports are within the last 10 years, yet crystalline silica has been studied in some fashion much longer than that. The most logical explanation is that most earlier studies were terminated after a few months, and the resulting observation periods were too short. It appears that silica-induced tumors in the rat are a late lifetime phenomenon which may be more related to chronological age than anything else.

In a recent review by Davis (1993), he states "The finding that quartz can be carcinogenic in rats but not in other experimental animals is part of a pattern which indicates that the rat lung responds to widespread chronic damage and fibrosis with tumor production much more readily than other species. This makes the prediction of carcinogenic hazard to humans very difficult, because results from rats tend to exaggerate danger levels, particularly when extremely high doses are used." Mauderly (1993) also expresses a number of uncertainties in using rat data to assess risk from human exposures to silica and other particles. "Perhaps the greatest uncertainty is the apparent propensity of rats to develop lung tumors when chronically exposed to respirable, poorly soluble dusts under conditions overloading dust clearance mechanisms and resulting in the progressive accumulation of large specific lung burdens of particles (mass of particle/mass of lung)." Existing data suggest that rats may not model human responses to heavy dust loading well (Mauderly, 1993). Moreover, it is unclear why rats develop lung cancers in response to a number of inert or nuisance dusts such as titanium dioxide, carbon black, toner, and shale (Oberdorster and Ferin, 1990).

There is no question that the laboratory rat is susceptible to lung tumor induction by certain forms of crystalline silica as well as a number of other particulates. It is also true that other common laboratory animals apparently are not. What this means for those considering limits on human exposure is far from clear as testing rodents for toxicity at high dose levels does not provide sufficient information for establishing reasonable risk levels based on predicted numbers of human cancers. Much regulatory policy is based on a non-threshold approach which has evolved from radiation biology where low thresholds are difficult to identify at best (Ames and Gold, 1991). Toxic response to chemicals, i.e. non-radioactive materials is related to dose, and until adequate dose response data are available, preferably from more than one species and supported by mechanistic data, it is premature to apply overly stringent minimum risk levels to such a ubiquitous material as crystalline silica. Workplace protection should be carefully done, but to apply the same stringency to

environmental situations where exposure is minimal would badly overstate any hazard.

Mechanistic Data

Lung tumors in silica-exposed rats are associated with fibrotic lesions, and a number of pathologists have emphasized that these are analogous to "foreign body" or scar tumors occurring in man. In this regard, there may be a causal association between the development of fibrosis and carcinogenesis as mechanistically, these are both diseases of altered cell proliferation and differentiation. Carcinogenesis, the process of tumor development, is a complex, multistage process which occurs in man over a long latency period of disease. The process is classically regarded as being initiated by an alteration in the DNA of the cell which can be inherited by daughter cells. Thus, an "initiator" is often regarded as a genotoxic substance, often causing a mutation in DNA, which can initiate the cancer process. However, it should be emphasized that genotoxic agents at high concentrations can result in cell death, and not all mutagens are carcinogens. Thus, interaction of a substance with the DNA of a cell does not always result in cancer nor necessarily render it a carcinogen.

It has been suggested that some forms of silica generate chemical reactions producing active oxygen species (AOS) due to their surface properties. For example some silica preparations, especially freshly crushed, catalyze the formation of AOS as measured by electron spin resonance (ESR) (Vallyathan et al, 1988). These AOS can then interact with DNA, protein, lipids (i.e. lipid peroxidation) and other macromolecules to damage cells or cause other cellular reactions. Silica particles are not mutagenic in bacterial mutagenicity assays or mammalian cells (summarized in IARC, 1987), but recent studies show oxidative DNA damage by Min-U-Sil 5 and α-quartz using isolated bacterial DNA in a DNA strand breakage assay (Daniel et al., 1993). Chemical bonding also appears to occur between silica and isolated DNA in a test tube (Saffiotti et al, 1993). Whether these observations are related to the toxic effects of silica in cells of the lung are questionable since cells normally have a cadre of antioxidant enzymes which protect against AOS and are induced after inhalation of silica by rats (Janssen et al., 1992). Moreover, oxidative DNA damage is also observed in isolated DNA after addition of iron salts, (as iron catalyzes the formation of AOS) (Toyokuni and Sagripanti, 1993). Thus to link this event directly to carcinogenicity is unmerited.

The Syrian hamster embryo (SHE) bioassay is one that is sensitive to mineral-induced cell transformation as opposed to other cell transformation assays which do not produce positive results (reviewed in Mossman et al., 1990). An earlier study showed a low transforming activity of two samples of α-quartz in comparison to either crocidolite or chrysotile asbestos (Hesterberg and Barrett, 1984). Unfortunately, negative control or inert particles were not used in these assays, and glass fibers, which are noncarcinogenic in man and rodents in chronic inhalation studies, also

tested positively to the same degree as asbestos. Subsequent analyses revealed a lack of chromosomal aberrations in SHE cells treated with α-quartz (Oshimura et al., 1984). However, sister chromatid exchanges (SCE) were observed in human lymphocytes (co-cultured with monocytes) with the highest of 3 doses of tridymite tested, but parallel studies using Min-U-Sil failed to reveal consistently increased SCE at various doses (Pairon et al., 1990). By contrast, neither Min-U-Sil nor tridymite caused SCE in isolated lymphocytes, and studies by Price-Jones et al. (1980) showed no increase in SCEs in Chinese hamster cells exposed to Min-U-Sil.

Recent studies using a BALB/3T3 mouse fibroblast transformation bioassay have revealed dose-dependent induction of transformed foci of cells with 5 samples of quartz (Saffiotti et al., 1993). Quartz-transformed foci of cells were injected into nude mice and caused tumors with several marker chromosomes unique to the quartz-treated cells. However the author states "several repeated tests of each sample would be needed to identify whether the relatively limited dose-response differences observed among different samples are reproducible and significant". Moreover, it will be important to evaluate comparative results with negative and positive control dusts, which may or may not have been included in these experiments. (Unpublished data).

Tumor promotion, a process in which initiated cells are propagated during carcinogenesis, may be a more plausible mechanism of silica in the carcinogenic process as epithelial cell hyperplasia is a common feature observed in the rat lung after inhalation of silica (reviewed in Holland, 1990). As stated by Saffiotti and Stinson (1988), "strikingly different patterns of epithelial response can be observed in different species " of rodents which may correlate directly to their fibrogenic and carcinogenic responses to silica. The pathways by which silica induces cell proliferation may be similar in epithelial cells and fibroblasts. Thus the processes of carcinogenesis and fibrosis may be functionally or causally related, and fibrosis may be required for the development of tumors as has been espoused by Craighead (1990), Kuschner (1987) and others. As emphasized recently by Collins and Marty (1993), " If silicosis, a non-malignant disease, must occur before cancer due to silica occurs, there would be a threshold for silicosis and for subsequent lung cancer. Thus, low environmental levels of silica below the threshold dose for silicosis would pose no cancer risk." These views are consistent with the data showing a threshold of response to both Min-U-Sil and tridymite in dose response studies in vitro (Pairon et al., 1990).

The induction of fibroblast proliferation by silica-exposed human macrophages in culture (Brown et al., 1988) supports a number of publications suggesting that cytokines or growth factors released by cells of the immune system may medicate the toxic, fibrogenic and hyperplastic effects of silica on epithelial cells and fibroblasts of the lung (Driscoll et al., 1990; Lugano et al., 1984; Miller and Hook, 1990; Panos et al., 1990). Complex interactions between lymphocytes, neutrophils and macrophages

may trigger secretion of proliferative factors into lung fluids (Lesur et al., 1992; Li et al., 1992; Melloni et al., 1993).

A recent paper showing alterations in the pulmonary microsomal cytochrome P-450 system after intratracheal administration of Min-U-sil to rats suggests a mechanism of co-carcinogenesis whereby silica might influence the lungs defense system to some chemical carcinogens (Miles et al., 1993). However, these alterations may be beneficial in that they metabolize and or deactivate these chemicals, and the authors urge "a link between these effects and the possible development of lung cancer in silicosis can not be made at this time".

Summary of Mechanistic Studies

In summary, studies above suggest that certain types of crystalline silica may generate AOS which then may mediate damage to isolated DNA and other macromolecules in a test tube, but the relationship of these phenomena to carcinogenesis is questionable in view of the weak transformation potential of silica in mammalian cell systems. A more plausible role of crystalline silica in tumor development in the rat is its ability to stimulate epithelial cell hyperplasia and mutagenesis after chronic, high-dose inhalation (Ames and Gold, 1991). Since a number of other particles induce inflammation and hyperplasia under similar regimens, this may be related to a nonspecific propensity of inhaled particles to cause tumors in the rat at high airborne concentrations. As emphasized by Witschi: "It is of course possible in every study with promoting agents (i.e. agents inducing cell proliferation) to find a threshold for the so-called promoting agent. Since tumor promotion does not appear to involve direct and immutable action with the genome and since there are certainly no human data on the effects of promoters, it is acceptable to claim the existence of thresholds for promoters." Unfortunately, the lack of dose response studies in most protocols in vivo and in vitro preclude the utility of mechanistic data in determining the existence of a threshold for genotoxic or proliferative responses to silica. However, some data suggest a NOAEL (No-Observed-Adverse-Effect Level) or threshold for cytogenetic effects (Oshimura et al., 1984) and SCE (Pairon et al., 1990).

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